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Capsular Contracture In Silicone Breast Implants: Insights From Rat Models

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ABSTRACT

Breast augmentation with silicone implants is one of the most common procedures performed by plastic surgeons around the world. Capsular contracture is a frequent complication in breast augmentation and reconstructive surgery, that requires invasive intervention. The inflammatory response to implanted mammary prostheses appears to be directly associated to capsular contracture. This review discusses the evidences from rat models studies, on the role of inflammation and fibrosis in capsular contraction and its relation to silicone breast implants surface.

Key words: capsular contracture, silicone breast implant, breast augmentation, smooth silicone implants, textured silicone implants, polyurethane-coated silicone implants.

INTRODUCTION

Plastic surgery had robust advances in the last decades, with the development of new surgical techniques and new materials used as substitutes of organs and tissues. Breast augmentation with silicone implants is one of the most common procedures performed by plastic surgeons in the world (Sukhova et al. 2012). Few medical materials were studied on their safety as rigorously as the silicone gel implants (Barnsley et al. 2006, Gampper et al. 2007, Spear et al. 2006). Silicone has been widely used in many areas of medicine demonstrating its biosafety and biocompatibility (Sukhova et al. 2012, Barnsley et al. 2006).

Czerny (1895) described the first breast augmentation procedure when reported the transplantation of a giant lipoma to the breast (Czerny 1895, Spear et al. 2009). There were numerous unsuccessful attempts of breast augmentation with both alloplastic and autologous tissue since then (Gersuny 1980, Thorek 1942, Harris 1961, Lalardrie and Mouly 1978, Rubin 1951, Edgerton and Mc 1958, Demergian 1963, Calnan 1970, Smahel et al. 1977). Silicone implants were first introduced in 1963 by Cronin and Gerow (Cronin and Gerow 1963), starting the modern era of breast augmentation (Young and Watson 2001, Adams 2009a, Spear et al. 2009).

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Five different generations of silicone implants have been developed (Maxwell and Gabriel 2009, Pitanguy 1991), as demonstrated in Table I.

The first generation of implants (1962-1970) was characterized by a dense and viscous silicone gel, surrounded by a thick, smooth implant shell. Second generation (1970-1982) was rounder, with less cross-linked gels (less viscous) covered by a smooth, thinner and slightly permeable shell (Calobrace and Capizzi 2014). In order to reduce capsular contracture, third generation implants (1982-1992) came with a more viscous gel and thicker either smooth or textured shell, and a less permeable low-bleeding elastomer barrier (Maxwell and Gabriel 2009). When the textured surface came up, the fourth-generation devices arised (1993 to present) (Adams 2009a). Texturing of implant surface was due to the experience with polyurethane (PU)-coated foam implants, which indicated that rough implants resulted in lower capsular contracture rates. Finally, cohesive silicone gel-filled implants can be considered fifth-generation devices (Adams 2009a, Maxwell and Gabriel 2009) (Table I). The updates in progressive generations have correlated with a decreased incidence in capsular contracture, although it is not clear if this is entirely because of implant design (Bengtson et al. 2007, Cunningham 2007, Danino et al. 2001).

Besides the evolution of silicone implants and surgical procedures, breast augmentation is still associated with complications such as hematoma, seroma, infection, rupture, silicone leakage, changes in mammary sensitivity, chronic pain, poor positioning, wrinkling skin, and capsular contracture (Barnsley et al. 2006, Spear et al. 2006, Thorek 1942., Harris 1961, Lalardrie and Mouly 1978, Garcia et al. 2002, Edgerton and Mc 1958, Demergian 1963, Calnan 1970). Capsular contracture is the formation of a fibrous scar tissue that surrounds a foreign body or surgically implanted device (Adams et al. 2006). Artificial

TABLE I
Evolution of silicone gel-filled breast implants.

Implant Generation	Period	Characteristics
First Generation	1962-1970	Thick, two-piece shell Smooth surface Anatomically-shaped (teardrop) Viscous silicone gel
Second Generation	1970-1982	Thin, slightly permeable shell Smooth surface Round shape Less viscous silicone gel
Third Generation	1982-1992	Thick, strong, low-bleed shell Smooth surface Round shape More viscous silicone gel
Fourth Generation	1993-present	Thick, strong, low-bleed shell Smooth and textured surfaces Round and anatomically-shaped More viscous (cohesive) silicone gel
Fifth Generation	1993-present	Thick, strong, low-bleed shell Smooth and textured surfaces Round and diverse anatomical shapes Enhanced cohesive and stable gel

joints, heart valves, central venous catheter ports, breast implants, and many additional medical devices have been involved in capsule formation and its adverse consequences (Adams et al. 2006). Capsule formation plays an important role in the host response against a foreign body. Therefore, the outcome of this process may pose a serious health risk and/or aesthetic sequelae (Adams et al. 2006). Mammary prostheses can induce inflammatory responses, periprosthetic fibrous capsule formation and implant encapsulation. Eventually, if capsular contracture occurs another surgical intervention is required for implant removal (Balderrama et al. 2009). Capsular contracture remains one of the most common complication and a leading cause for patient dissatisfaction of both aesthetic and reconstructive breast implant surgery (Lee et al. 2014, Wong et al. 2006).

Predisposition to hypertrophic scar and declining age have been associated to capsular contracture, hematoma and silicone gel bleed (Adams 2009b, Vieira et al. 2010). Several studies also evidence the link between subclinical infection and capsular contracture occurrence (Bergmann et al. 2014, Del Pozo et al. 2009, Dobke et al. 1995). In the same line, many studies support that bacterial biofilms on breast implants, most commonly formed by *Staphylococcus epidermidis*, can promote chronic inflammation, and stimulate fibrosis and capsular contracture (Rieger et al. 2013, van Heerden et al. 2009, Dobke et al. 1995, Netscher 2004). Del Pozo et al. (2009), in a prospective observational assay verified bacterial infection in breast prostheses from 45 patients who underwent implant removal for reasons other than overt infection. The results reveal a significant association between capsular contracture and the presence of skin flora bacterias on the implant (Del Pozo et al. 2009). Recently, Bergmann et al. (2014) used a rat model to evaluate the influence of controlled infection in capsular formation around PU-coated silicone implants, and demonstrated that both implant surface and bacterial contamination impact the architecture of capsule formation (Bergmann et al. 2014). This approach showed that bacterial infection leads to thicker capsules with increased inflammatory response evidenced by the higher amount of inflammatory cells within the tissue (Tables II and III) (Bergmann et al. 2014). However, Mendes et al. (2008) also using a rat model, observed no relationship between *Staphylococcus epidermidis* infection and capsular architecture (Table II and III) (Mendes et al. 2008). Therefore, the possible relationship of bacterial infection and capsular contracture occurrence needs further study.

Many studies are committed in unveiling not only the causes but also the possible preventive strategies to capsular contracture (Moreira et al. 2009, Poeppl et al. 2007, Ibrahim Canter et al. 2007, Bern et al. 1992, Vieira et al. 2010, Adams et al. 2006). As showed in Table I, silicone implants underwent several structural adjustments in the last decades in order to diminish foreign body reaction and consequently reduce capsular contraction incidence (Balderrama et al. 2009). Among other modifications, smooth surface implants were replaced by textured linings or PU-coating (Lyras 1993). However, despite these changes in implant surface being reported by many authors as crucial in reducing capsular contracture, this approach is controversial (Pollock 1997, Spear et al. 2000, Ersek 1991). The real cause of capsular contracture remains elusive (Rohrich et al. 1999). This review discusses the evidences obtained from rat models of silicone breast implants, on the role of inflammation and fibrosis in capsular contraction pathogenesis and their relation to the silicone prosthesis surface.

Experimental Rat Models for Capsular Contracture Study

Numerous experimental studies have attempted to identify the reason behind the lower rates of capsular contracture in textured surface implants. These

TABLE II
Summary of experimental approaches used to study capsular contracture after implantation of silicone mini-prostheses in rats.

Reference	Title	Study Design
Bastos et al. 2007	***"Histologic analysis of zafirlukast's effect on capsule formation around silicone implants".***	**Animals:** 32 adult female *Wistar* rats. **Groups:** 3 groups that received both **smooth** and **textured** surface silicone mini-implant. **Intervention:** Intraperitoneal treatment with either vehicle or zafirlukast (1.25 or 5 mg/kg/day; for 90 days). **Follow up:** 90 days. **Capsular evaluation:** Histological (HE, trichrome and picrosirius red stain), and immunohistochemistry (anti-α-SMA antibody) analyses.
Bastos et al. 2012	***"Effect of zafirlukast on capsular contracture around silicone implants in rats".***	**Animals:** 40 adult female *Wistar* rats. **Groups:** 4 groups that received both **smooth** and **textured** surface silicone mini-implant. **Intervention:** Intraperitoneal treatment with either zafirlukast (1.25 mg/kg/day; during 90 days) or vehicle**.** **Follow up:** 90 days. **Capsular evaluation:** Intra-implant pressure measurement.
Bergmann et al. 2014	***"The effect of a bacterial contamination on the formation of capsular contracture with polyurethane breast implants in comparison with textured silicone implants: an animal study".***	**Animals:** 80 adult female *Wistar* rats. **Groups:** 4 groups that received either **textured s**urface or **PU-coated** silicone mini-implant. **Intervention:** Implant inoculation with vehicle or a standard volume of *Staphylococcus epidermidis*. **Follow up:** 60 days. **Capsular evaluation:** Histological (HE, trichrome, naphthol-ASD-acetatesterase and picrosirius red stain), immunohistochemistry (anti-CD3, anti-CD138, anti-Lysozyme, anti-Pax5 and anti-α-SMA antibodies), and microbiological analyses.
Cardenas-Camarena et al. 2005	***"Electrostimulation: uses and applications for periprosthetic capsular contracture: experimental model".***	**Animals:** 40 adult female *Wistar* rats; **Groups:** 10 groups that received both **smooth** and **textured** surface silicone min-implant. **Intervention:** Different protocols of local electrostimulation from the 3rd to the 15th postoperative day. **Follow up:** 16 days; **Capsular evaluation:** Histological (HE) analyses.
Gancedo et al. 2008	***"Pirfenidone prevents capsular contracture after mammary implantation".***	**Animals:** 20 adult female *Wistar* rats. **Groups:** 2 groups that received both **smooth** and **textured** surface silicone mini-implant. **Intervention:** Intraperitoneal treatment with vehicle or Pirfenidone (PFD) (200 mg/Kg/day, for 60 days). **Follow up:** 60 days. **Capsular evaluation:** Histological (HE, trichrome, picrosirius red stain), immunohistochemistry (anti-TGF-β1, anti-α-SMA antibodies), and real-time PCR (TGF-β and collagen αI) analyses.
Mendes et al. 2008	***"Histological study on acute inflammatory reaction to polyurethane-coated silicone implants in rats".***	**Animals:** 35 adult female *Wistar* rats. **Groups:** 7 groups that received **PU-coated** silicone mini-implant. **Intervention:** Contamination of implant cavity with 10^1, 10^3, or 10^5 bacteria/mL with implant immersions in anti-microbial solution or saline**.** **Follow up:** 30 days. **Capsular evaluation:** Histological (HE and picrosirius red stain) analyses.

TABLE II (continuation)

Reference	Title	Study Design
Vieira et al. 2010	***"Vascular endothelial growth factor overexpression positively modulates the characteristics of periprosthetic tissue of polyurethane-coated silicone breast implant in rats".***	**Animals:** 34 adult female *Wistar* rats. **Groups:** 4 groups that received **textured** surface or **PU-coated** silicone mini-implant. **Intervention:** no intervention. **Follow up:** 30 and 60 days. **Capsular evaluation:** Histological (HE, trichrome, picrosirius red stain), immunohistochemistry (anti-VEGF, anti-TGF-β1, anti-α-SMA, and anti-MPX antibodies) analysis.
Zimman et al. 2007	***"The effects of angiotensin-converting-enzyme inhibitors on the fibrous envelope around mammary implants".***	**Animals:** 24 adult female *Wistar* rats. **Groups:** 4 groups that received either **smooth** or **textured surface** silicone mini-implants. **Intervention:** angiotensin-converting enzyme inhibitor enalapril administered in drinking water, *ad libitum*. **Follow up:** 90 days. **Capsular evaluation:** Histological (HE, trichrome, picrosirius red stain), and immunohistochemistry (anti-TGF-β1 and anti-collagen type III antibodies) analysis.

HE (Hematoxylin-eosine); MPX (myeloperoxidase); Pax5 (paired box protein 5); PU (polyurethane); TGF-β1 (transforming growth factor beta 1); VEGF (vascular endothelial grown factor); α-SMA (alpha smooth muscle actin).

TABLE III
Summary of conclusions from capsular contracture studies after implantation of silicone mini-prostheses in rats.

Reference	Conclusions
Bastos et al. 2007	Systemic leukotriene receptor antagonist (Zafirlukast) treatment reduced inflammatory parameters, myofibroblasts, collagen density and capsular thickness in periprosthetic tissue of animals with textured surface silicone prostheses. Treatment with leukotriene antagonist had no effect in capsular tissue of smooth silicone implants.
Bastos et al. 2012	Systemic Zafirlukast treatment reduces capsular contracture-related factors, surrounding textured silicone implants only. Results suggest that smooth and textured surface silicone prostheses have different mechanisms to induce capsular contracture.
Bergmann et al. 2014	Bacterial infection induces thicker capsule formation and increases inflammatory response. PU-coated implants drives thicker capsule formation and intense local inflammatory processes when compared to textured implants. However, periprosthetic tissue surrounding PU implants showed lower expression of parallel myofibrils.
Cardenas-Camarena et al. 2005	Local electrostimulation regulates periprosthetic capsule formation in both textured and smooth surface silicone prostheses when transplanted into rats.
Gancedo et al. 2008	Systemic treatment with Pirfenidone (PFD), an anti-fibrotic drug used for pulmonary fibrosis, decreases inflammation, TGF-β1 levels, and capsular thickness, compared with vehicle-treated animals. Histological analysis shows no differences between textured and smooth periprosthetic tissue.
Mendes et al. 2008	PU-coated silicone implants induce inflammatory response in periprosthetic tissue histologically-patterned as chronic foreign body granulomas. Histological changes induced by *Staphylococcus epidermidis* inoculation were dose-independent.
Vieira et al. 2010	Periprosthetic tissue of PU-coated silicone implants was thicker and showed intense vascularization and inflammatory response, compared with textured implants. In addition, PU-coated implants had a softer capsule and increased VEGF and TGF-β1 levels in capsular tissue than textured surface prostheses.
Zimman et al. 2007	Systemic enalapril treatment reduced inflammatory and fibrotic processes in the periprostethic tissue from both textured and smooth surface silicone implants.

PU (polyurethane); TGF-β1 (transforming growth factor-beta 1); VEGF (vascular endothelial growth factor).

studies have used animal models with smooth or textured prostheses implanted both subcutaneously and submuscularly, with subsequently histological evaluation of the neo-formed periprosthetic tissue (Barone et al. 1992, Bucky et al. 1994, Bern et al. 1992, Clugston et al. 1994, Brohim et al. 1993b). Importantly, some studies found tighter and thicker capsules surrounding textured implants compared to smooth implants (Barone et al. 1992, Bucky et al. 1994, Bern et al. 1992), while others demonstrated that capsular contracture is less often in textured surface implants (Clugston et al. 1994, Brohim et al. 1993b).

Despite these ambiguous results, miscellaneous of clinical data on capsular contracture incidence in patients (Barnsley et al. 2006), highlights the relevance of controlled experimental models to study capsular contracture etiology and many assays rely on animal models to mimic human periprosthetic capsular contracture (Barnsley et al. 2006, Wong et al. 2006, Vieira et al. 2010). Preclinical benchwork advantages include the control of the experimental environment, minimizing unwanted variables, besides being a faster, less expensive approach (Bastos et al. 2003, Bucky et al. 1994, Clugston et al. 1994, Imber et al. 1974, Ksander et al. 1981, Peters et al. 1980, Vieira et al. 2010). Animals such as pigs, rabbits, dogs, rats, and mice have been used with variable results (Clugston et al. 1994, Fagrell et al. 2001, Ajmal et al. 2003, Shah et al. 1981, Kossovsky et al. 1984, Chen et al. 1996, Darouiche et al. 2002, Ksander et al. 1981, Tang et al. 1998, Adams et al. 2006, Marques et al. 2012, Brohim et al. 1993a, Minami et al. 2006, Park et al. 2013, Moyer et al. 2012, Bastos et al. 2003, 2012), but it is consensus that the rat is the most appropriate animal model that provides relevant scientific conclusions with accurate histological extrapolation to the human tissue (Czerny 1895b, Harris 1961, Lalardrie and Mouly 1978, Garcia et al. 2002). In addition, most studies agree that a 90-days follow up seems to be suitable to evaluate capsular contracture in rats (Tables II and III). The main approaches tested in the studies reviewed in Tables II and III were the effects of smooth and/or textured silicone implants on different histological and biochemical parameters (Zimman et al. 2007, Vieira et al. 2010, Mendes et al. 2008, Gancedo et al. 2008, Cardenas-Camarena et al. 2005, Bergmann et al. 2014, Bastos et al. 2007b, 2012). The results indicate different degrees of fibrosis, fibroblast activation, inflammation, and capsule thickness in periprosthetic tissue (Tables II and III) (Frangou and Kanellaki 2001, Eltze et al. 2003, Minami et al. 2006, Eltze et al. 2006, Adams et al. 2006, Cardenas-Camarena et al. 2005, Gancedo et al. 2008, Chelko et al. 2012, Aparecida da Silva et al. 2014, Vieira et al. 2010). Some authors did not find histological differences between smooth and textured implants surrounding tissue (Gancedo et al. 2008), but most found thicker capsules with increased cellularity and less frequent contractures in the textured surface (Bastos et al. 2007a, 2012, Zimman et al. 2007, Cardenas-Camarena et al. 2005, Bergmann et al. 2014) (Tables II and III). There are some studies with rabbits trying to understand the capsular contracture process, but interestingly, most of them use smooth surface mini-implants only (Shin et al. 2013, Park et al. 2013, Moyer et al. 2012, Adams et al. 2006). To our knowledge, a single rabbit study compared textured and smooth surface silicone mini-implant, and found less cellularity and reduced capsule thickness surrounding textured surface prostheses (Uzunismail et al. 2008). Minami et al. (2006) used pigs to show that capsular contracture in smooth implants have a significantly higher intra-implant pressure, and the smooth implant capsule was significantly thicker than the textured (Minami et al. 2006).

Considering that prevention of capsular contracture is a relevant clinical approach, various experimental designs using rats as model have been conducted aiming to identify potential pharmacological targets to achieve that goal, testing

different implant materials (i.e. textured, smooth or PU-covered) (Chang et al. 1992, Ersek 1991, Hester et al. 1988, Asplund et al. 1996, Thuesen et al. 1995), surgical procedures (i.e. subglandular or submuscular pockets) (Puckett et al. 1987, Hakelius and Ohlsen 1997, Handel et al. 1995), and drug delivery systems (Ajmal et al. 2003, Lemperle and Exner 1993). Tables II and III show some studies that evaluated the effect of angiotensin-converting enzyme inhibitors (Zimman et al. 2007), leukotriene receptor antagonist (zafirlukast) (Bastos et al. 2007b, Bastos et al. 2012), and anti-fibrotic compound (pirfenidone) (Gancedo et al. 2008) on biochemical and cellular features of periprosthetic tissue from rats that received smooth or textured silicone implants (Bastos et al. 2007b, 2012, Gancedo et al. 2008, Zimman 2007). Bastos et al. (2012) also tested the effects of Zafirlukast on intra-implant pressure after implantation of both textured and smooth silicone implant in rats, and concluded that treatment increases internal pressure only in textured silicone implants (Tables II and III). Finally, these distinct pharmacological outcomes on capsular prevention strengthen the concept that capsular contracture pathophysiology is prosthesis type-dependent (Bastos et al. 2007b, 2012, Gancedo et al. 2008, Zimman 2007, Bergmann et al. 2012, 2014).

Our previous study on the characteristics of periprosthetic tissue surrounding textured surface silicone implants in rats demonstrated that PU-coated implants induce thicker capsules, associated to intense "foreign body" immune reaction and up-regulation of vascular endothelial growth factor (VEGF) (Vieira et al. 2010). We propose that high vascularization induced by VEGF results in this thicker capsule, but capsular enlargement would be due to an increase of the non-collagenoustissue layer. Furthermore, we concluded that stimulation of an angiogenic response in periprosthetic tissue leads to a softer capsule surrounding the silicone implant, which should decrease capsular contracture occurrence in breast reconstruction and augmentation (Vieira et al. 2010). Consistent with our findings, other studies also hypothesized that the positive effects of PU implants on capsular prevention are mainly related to the biochemical effects of the biomaterial in the surrounding tissue rather than the prosthesis surface texture itself (Adams 2009a, Hester et al. 1988, 2001, Lilla and Vistes 1976, Brand 1984, Dunn et al. 1992, Brohim et al. 1992, Batra et al. 1995, Picha and Goldstein 1991, Picha et al. 1990, Sank et al. 1993, Santere et al. 2005, Bucky et al. 1994, Rebello 1996).

CONCLUSIONS

Capsular contracture is a multifactorial process involving inflammatory responses that results in exacerbated fibrotic reaction in silicone breast implant surrounding tissue. However, both the precise trigger and the mechanisms underlying capsular contracture are still unclear. Several animal models have been described in order to approach normal capsular formation, but the origin of capsular contracture can hardly be predicted and the mechanisms concerning pathological capsule formation have yet to be evaluated in these models.

Some animals such as rabbits, pigs and mice have been used with variable results, but it is consensus that rats provide a reproducible and relatively cheap model with accurate histologic extrapolation to human tissue. The results of numerous experimental approaches have shown variations in capsule thickness with different intensities of fibrosis and inflammation in periprosthetic tissue of both textured and smooth silicone implants. Contradictory experimental findings, at least in part, may be due to characteristics of implant manufacturer, consistency of the silicone gel, shape of the implants, (Minami et al. 2006, Calobrace and Capizzi 2014, Adams 2009a, Kjoller et al. 2001, Henriksen et al. 2005, Steiert et al. 2013), size of the pores, type of elastomer surface (Brohim et al. 1992), and/or relatively short observation windows

(Minami et al. 2006, Clugston et al. 1994). Herein, we showed that the mean follow up used in most assays is 90 days. Therefore, long-term studies using rat models might be necessary to translational conclusions, especially if one considers that 15 years of follow up in a female human being is comparable to approximately 9 months in rat models (Vieira et al. 2010).

In addition, since experimental models are rarely able to replicate the development of capsular contracture, most studies evaluate the outcome of different interventions on normal capsule formation in their animal models (Vieira et al. 2010, Dobke et al. 1995, Rieger et al. 2013, Bastos et al. 2003, 2007a, Imber et al. 1974, Ksander et al. 1981, Peters et al. 1980, Chelko et al. 2012, Aparecida da Silva et al. 2014, Shin et al. 2013, Uzunismail et al. 2008, Chang et al. 1992, Hester et al. 1988, Asplund et al. 1996, Thuesen et al. 1995, Puckett et al. 1987, Hakelius and Ohlsen 1997, Handel et al. 1995, Lemperle and Exner 1993, Zimman 2007, Zimman et al. 2007, Bergmann et al. 2012, Hester et al. 2001, Lilla and Vistes 1976, Brand 1984). This fact understates the impact of conclusions from previous studies, since therapy should be focused in pathologic capsule formation. Some authors evaluated parameters such as liquid infusion and pressure-volume curve or applanation tonometry, beyond the histological analysis to assess capsular contracture in animal models (Bastos et al. 2012, Bucky et al. 1994, Clugston et al. 1994, Peters et al. 1980, Adams et al. 2006, Marques et al. 2012, Minami et al. 2006, Moyer et al. 2012). These studies contribute to the correlation of capsule histological analysis with dynamic pressure assays advancing our comprehension of capsular contracture. To our knowledge, only eight experimental studies showed indirect presence of the capsular contracture until now (Bastos et al. 2012, Bucky et al. 1994, Clugston et al. 1994, Peters et al. 1980, Adams et al. 2006, Marques et al. 2012, Minami et al. 2006, Moyer et al. 2012).

The translational potential of capsular contracture animal models still needs to be clarified. However, pre-clinical studies enable a more controlled and thorough assessment of the periprosthetic tissue characteristics, which is critical to our understanding on how silicone implant surface interacts with the surrounding tissue. Finally, these advances can open new avenues on implant type selection, and in prevention and/or treatment of symptomatic cases of capsular contracture.

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