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Breast

Aseptic versus Sterile Acellular Dermal Matrices in Breast Reconstruction: An Updated Review

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Background: As the use of acellular dermal matrices in breast reconstruction has become more commonplace and efforts are made to improve on postoperative outcomes, the method of acellular dermal matrix (ADM) processing (aseptic versus sterile) has become a subject of interest. This article provides an updated overview of the critical aspects of ADM processing in addition to application of ADMs in single- and two-stage breast reconstruction, a review of the morbidity associated with ADM use, and alternatives.

Methods: A literature review was performed in PubMed identifying recent systematic reviews, meta-analyses, and head-to-head comparisons on aseptically processed ADM and sterile-processed ADM in implant-based breast reconstruction.

Results: Recent meta-analyses have shown a 2- to 3-fold increase in infections and tissue expander/implant explantation rates and a 3- to 4-fold increase in seroma formation compared with non-ADM reconstruction techniques. Comparisons of aseptic and sterile ADMs in multiple studies have shown no significant difference in infection rates and equivocal findings for other specific complications such as seroma formation.

Conclusions: Current evidence on the impact of processing techniques that improve ADM sterility on postoperative morbidity in implant breast reconstruction is unclear. Deficiencies of the available data highlight the need for well-designed, multicenter, randomized controlled studies that will aid in optimizing outcomes in implant-based breast reconstruction. *(Plast Reconstr Surg Glob Open 2016;4:e823; doi: 10.1097/GOX.0000000000000819; Published online 22 July 2016.)*

Over 232,000 new cases of invasive breast cancer were diagnosed in the United States in 2013.[1] Although nearly 40% of women diagnosed with breast cancer ultimately undergo a total mastectomy, historically less than one quarter of these patients pursue immediate breast reconstruction.[2–8] Among women who undergo breast reconstruction, over 70% of operations use a tissue expander/implant (TE/I)–based technique,[9–12] and a majority of these cases incorporate the use of an acellular dermal matrix (ADM).[13]

Since the first reported application of ADM in breast reconstruction in 2005,[14] the indications for its use in breast reconstruction have expanded dramatically. ADM is used routinely by plastic surgeons for aesthetic and revisionary breast surgery, nipple reconstruction, single-stage breast reconstructions, and primary TE/I reconstructions.[15] Of the approximately 57,000 TE/I-based reconstructions performed annually in the United States, biologic mesh was used in nearly 56% of all cases.[11,13,16]

In trying to gain a better understanding of factors that influence the morbidity associated with use of ADMs in breast reconstruction, the method of ADM processing (aseptic versus sterile processing) has become a subject of interest with conflicting results from recent studies.[17–21] Whether ADM sterility has an impact on postoperative outcomes is the question at hand, and this article attempts to summarize the current literature and to identify gaps in our knowledge. Furthermore, this article provides an updated overview of the critical aspects of ADM processing in addition to application of ADMs in single- and two-stage breast reconstruction. A review of the morbidity associated with ADM use and alternatives is also presented.

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ACELLULAR DERMAL MATRICES IN BREAST RECONSTRUCTION

ADM offers several advantages when compared with the more traditional dual-plane and total submuscular reconstruction techniques for breast reconstruction.[19,22] Advantages include decreased inferior pole rippling and contour abnormalities, greater TE/I control within the mastectomy pocket, improved inferolateral pole coverage, avoidance of serratus fascia/musculature elevation, greater intraoperative expander fill and potentially fewer in-office expansions, improved aesthetic outcomes, and decreased capsular contracture.[15,19,22–30] Some of these advantages have made possible the addition of a single-stage reconstruction technique to the reconstructive armamentarium.

Single-stage breast reconstruction, although in many cases a misnomer, bypasses the previously unavoidable tissue expansion stage of implant breast reconstruction. The ADM allows for immediate placement of a full-size implant at the time of mastectomy—acting as an inferior and inferolateral extension of the pectoralis major muscle—obviating the need for expansion of the submuscular pocket. In appropriately selected patients with adequate skin preservation at the time of mastectomy, the use of ADM offers an attractive option and simplifies the overall reconstruction process (Fig. 1).[15]

The well-established two-stage breast reconstruction technique continues to be the more common form of implant-based breast reconstruction. Here again, ADM is used to provide support and coverage of the inferolateral pole[15,25,31] with benefits of greater control of the inframammary fold and reduced lateral migration of the prosthesis during expansion (Fig. 2).[14,15,25,31] Compared with the total submuscular coverage technique, several studies have reported increased intraoperative expander fill volumes with the use of ADM resulting in fewer in-office fills and a potentially shortened time to definitive reconstruction with expander–implant exchange.[15,25,28,32,33]

Although clearly beneficial, the overwhelming evidence indicates that ADM use in breast reconstruction increases postoperative morbidity when compared to similar implant reconstructions without ADM.[16,34,35] However, with the evolution and growth in the number and variety of available ADM products, questions exist on the effect of processing on postoperative morbidity.

ADM PROCESSING—ASEPTIC VERSUS STERILE

Aseptic processing refers to the technique of preventing, restricting, or minimizing contamination of a medical product with microorganisms from the environment, processing personnel, and/or equipment.[17,36] For ADM, this often includes proprietary semicontained processes of washing the allograft with detergents, antibiotics, and mechanical means that ensure near complete decellularization and decontamination (Fig. 3).[36] For example, AlloDerm is an aseptically processed ADM, which is treated with buffered salt solutions to remove the epidermis and is further subjected to mild, nondenaturing detergent

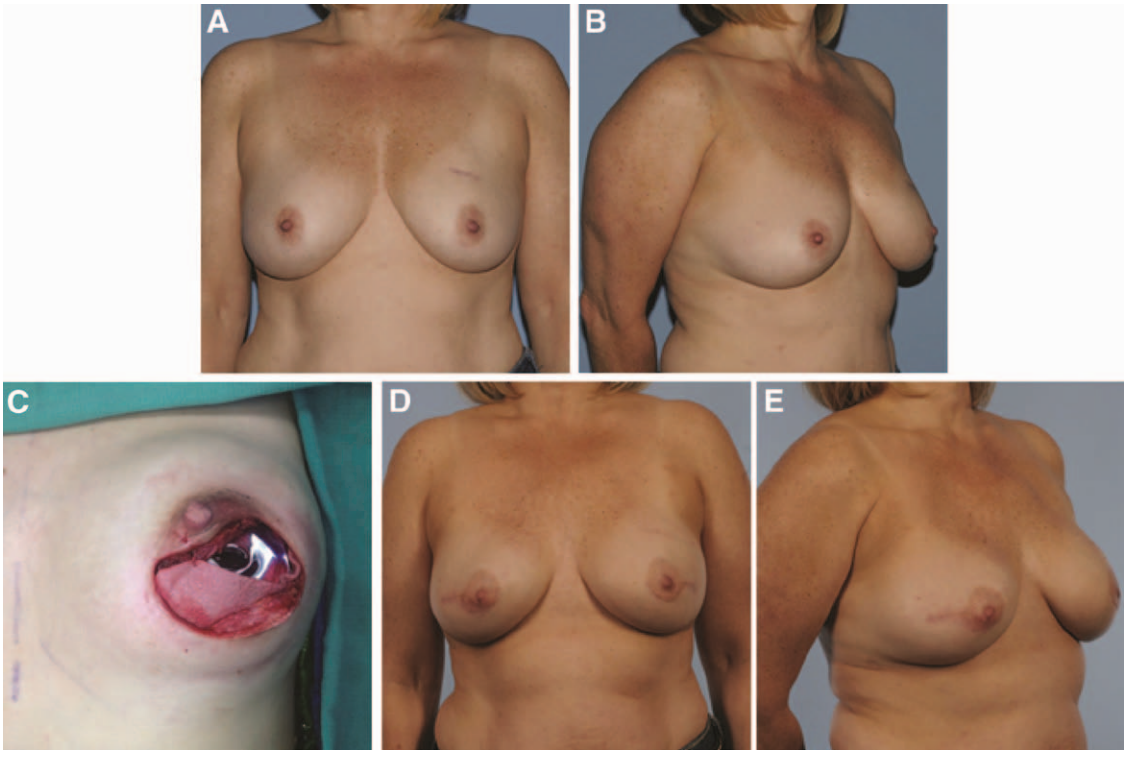

Fig. 1. Patient with a high risk of breast cancer with grade I ptosis of the breasts (A and B), periareolar incision for nipple-sparing prophylactic mastectomies with placement of silicone implant underneath pectoralis major muscle and acellular dermal matrix (C); and 6 mo after single-stage implant breast reconstruction (D and E).

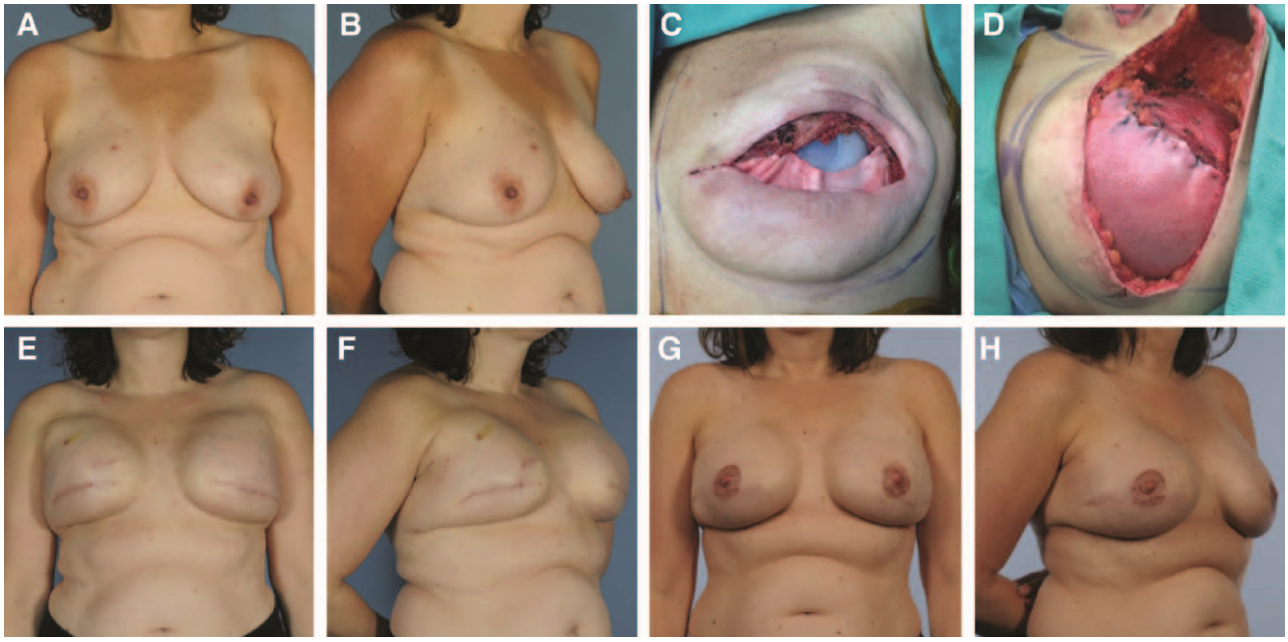

Fig. 2. Patient with right breast ductal carcinoma in situ and grade II ptosis of the breasts (A and B); subpectoral placement of tissue expanders with acellular dermal matrix for inferior pole coverage after skin-sparing mastectomies with expander partially filled intraoperatively (C and D); results after completion of expansion process (E and F); and final postoperative results after exchange of expanders for silicone implants, nipple reconstruction, and tattooing (G and H).

agents to eliminate remaining epidermal and dermal cells while maintaining the integrity of the collagen matrix.[37,38] Batches of ADM, processing solutions, and equipment are randomly sampled and extensively cultured to monitor for viable microorganisms using standards set by the US Pharmacopeia-71 sterility tests.[39] The US Pharmacopeia-71 sterility testing procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized, as this is ensured primarily by validation of the sterilization process or of the aseptic processing techniques.[29] Some companies culture the ADM before and after processing and even purposely inoculate their product with known quantities of organisms before processing to calculate the log reduction in viable organisms to further validate their processes. Aseptic processing is common for pharmaceuticals and heat/chemical/radiation-sensitive medical devices and products. Aseptically processed items generally do not have an associated sterility assurance level (SAL) because they do not undergo a validated terminal sterilization process and are thus not labeled on the package as "sterile" (Table 1).

Sterile ADM, however, has undergone a validated terminal sterilization process after initial cleansing and decellularization (Fig. 3). For biologic tissues, the most common terminal sterilization techniques include treatment with gamma radiation, electron beam radiation, chemical sterilization solutions, or ethylene oxide. Each method has distinct advantages/disadvantages and all are known to alter protein/collagen structure that can impact tissue incorporation and mechanical properties.[19,36,40] These alterations are usually dose-dependent, and newer sterilization processes can partially mitigate some of the detrimental effects. It has previously been shown that increasing gamma radiation doses in allograft material can cause increased scission of peptide bonds within collagen molecules, leading to reduced allograft tissue strength.[40] This damage can be limited by using extremely low temperatures, free radical scavengers, or by freeze-drying the graft before the sterilization process.[36,40] Theoretically, degradation of the allograft tissue's mechanical properties from high doses of gamma radiation could lead to TE/I malposition and worsened aesthetic outcomes. Complete sterility (i.e., the total absence of microorganisms) is not feasible nor practical when it comes to allografts or biologic tissues that are heat sensitive and cannot be autoclaved or radiated at high doses. Currently, a SAL of 10^{-6} is widely accepted as the definition of "sterile."[17,36,41] The SAL of 10^{-6} can be explained as the probability of 1 per 1,000,000 sterilized items having a viable microorganism after the sterilization process.[17] Because of the dose-dependent relationship between terminal sterilization and allograft damage, some biologic tissues are terminally sterilized to a lower SAL such as 10^{-3}, which theoretically offers the advantage of some level of sterility with less allograft compromise. However, this has not yet been experimentally proven in the published literature.

COMPLICATIONS WITH ASEPTIC VERSUS STERILE ADM BREAST RECONSTRUCTION

The current literature comparing sterile ADM to aseptically processed ADM in breast reconstruction is limited and has shown mixed results. Table 2 and Fig. 4 compare the outcomes of these studies and also include studies utilizing xenograft ADMs, which have always required terminal sterilization.[42,43] In a prospective multicenter cohort

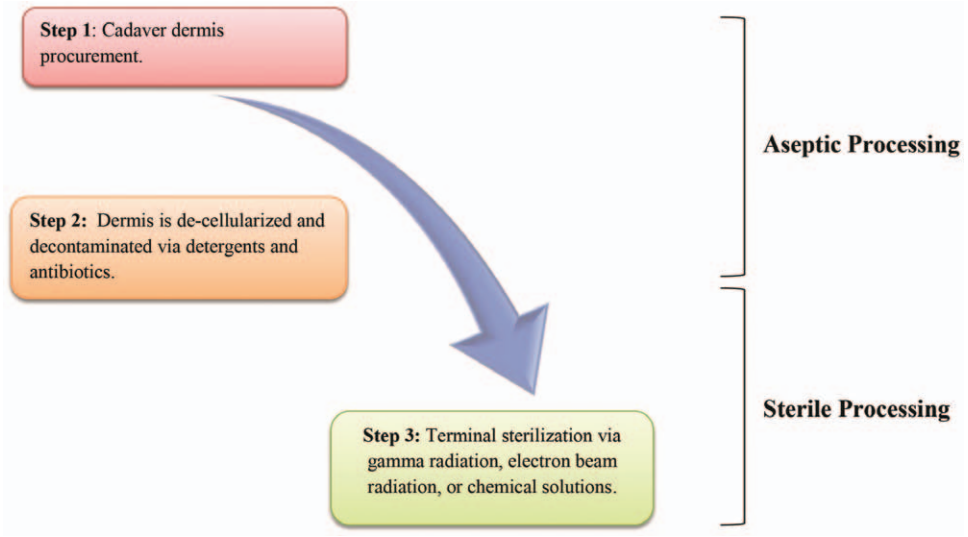

Fig. 3. Schematic outline of processing for aseptic and sterile acellular dermal matrices.

Table 1. Acellular Dermal Matrix Properties and Sterility Comparison

Product	Company	Source	Sterile	SAL	Cost per sq cm ($)	Method of Sterilization
*Alloderm (freeze-dried)	LifeCell	Human	No	NA	31.25	Aseptically processed
*Alloderm (ready to use)	LifeCell	Human	Yes	10^{-3}	31.25	Electron beam irradiation (low dose)
*Allomax	Bard (Davol)	Human	Yes	10^{-6}	29.15	Tutoplast process, γ-irradiation (low dose)
Strattice	LifeCell	Porcine	Yes	10^{-3}	26.94	Electron beam irradiation
DermACELL	Lifenet	Human	Yes	10^{-6}	34.00	Gamma irradiation
*DermaMatrix (off market)	Synthes/MTF	Human	No	NA	28.93	Aseptically processed
Flex HD Structural	Ethicon/MTF	Human	No	NA	27.31	Aseptically processed
*Flex HD Pliable	Mentor/MTF	Human	No	NA	27.31	Aseptically processed
Permacol	Covidien	Porcine	Yes	10^{-6}	21.63	γ-irradiation
PriMatrix	TEI Biosciences	Fetal bovine	Yes	10^{-6}	31.00	Ethylene oxide, silver ions
Repriza	SSP/Promethian Life Sciences	Human	Yes	10^{-6}	25.63	γ-irradiation
SurgiMend PRS	TEI Biosciences	Fetal bovine	Yes	10^{-6}	23.00	Ethylene oxide
XCM Biologic	Synthes/Ethicon	Porcine	Yes	10^{-6}	24.25	γ-irradiation

Cost based on estimate for Memorial Medical Center, Springfield, Ill.
*Denotes most commonly used types in breast reconstruction.
MTF, Musculoskeletal Transplant Foundation; NA, not applicable.

study evaluating staged breast reconstruction with the sterile-processed ADM Allomax (Davol Inc, Warwick, R.I.), Venturi et al[17] demonstrated a favorable complication profile. Over 12 months of follow-up of 65 breast reconstructions, they encountered one case of cellulitis (1.5%), two cases of partial flap necrosis (3.0%), and no cases of seromas or explantation.[17] Unfortunately, the study did not include an aseptic ADM control group for direct comparison and attempted to compare their outcomes to previously published studies on aseptically processed ADM.[9,26] Differences in patient demographics, comorbidities, and treatment variables limited the effectiveness of the attempted comparisons.

A direct comparison of LifeCell's (Branchburg, N.J.) aseptic ADM (freeze-dried [FD] AlloDerm) to their sterile ADM (AlloDerm ready-to-use [RTU]) was performed retrospectively by Buseman et al.[18] They found a statistically significant increase in seroma rates in the sterile Alloderm RTU group ($P = 0.003$), but no differences in infection rates. Similar findings were reported by Yuen et al,[20] who retrospectively reviewed their outcomes after switching from aseptic FD AlloDerm (n = 51 patients) to sterile AlloDerm RTU (n = 52 patients). They also found higher seroma rates, in addition to higher cellulitis rates, in the AlloDerm RTU group compared with FD Alloderm (22.0% vs 18.8%; $P = 0.599$ and 21.0% vs 12.5%; $P = 0.129$, respectively). These findings, however, did not reach statistical significance.

In contrast, a prospective cohort study by Weichman et al[19] comparing total submuscular coverage (351 breasts), aseptic AlloDerm (90 breasts), and sterile AlloDerm RTU (105 breasts) showed significantly fewer infections in the sterile group compared with the aseptic group (8.5% vs 20 %; $P = 0.0088$). Patients in the sterile group had a similar infection rate to the total submuscular coverage group (8.5% vs 5.7%; $P = 0.36$).[19] Interestingly, they noted less incorporation of the sterile ADM during the implant exchange operations compared with aseptic ADM. Notable limitations with this study included a significantly higher body mass index in the patients who had reconstruction with aseptic Alloderm and the potential

Table 2. Studies Comparing Aseptically Processed to Sterile-processed ADM in Breast Reconstruction

Study	Study and Patient Characteristics								Complications and Outcomes					
	Study Design	ADM Type	No. of Breasts	Mean Age, yr	Mean BMI	Diabetes, %	Smokers, %	Chemo, %	XRT, %	Complications, %	Seroma, %	Hematoma, %	Infections, %	Skin Necrosis, %	TE Removal, %
Buseman et al[18]	Retrospective review	AlloDerm	25 Pts	48	26.5	NA	28.0	44.0	0.0	NA	8.0	NA	16.0	NA	NA
		AlloDerm RTU	9 Pts	49.6	25.7	NA	33.0	11.0	11.0	NA	66.0	NA	11.0	NA	NA
Butterfield[42]	Retrospective review	SurgiMend	351	48.6	27	1.0	7.0	54.0	6.0	22.5	8.6	1.1	4.8	11.1	8.3
		AlloDerm	89	47.5	26.3	5.0	12.0	47.0	6.0	24.7	15.7	0.0	6.7	3.4	11.2
Glasberg and Light[43]	Retrospective review	AlloDerm	126	44.5	27.9	8.3	17.7	56.3	16.7	21.4	12.7	1.6	2.4	0.0	2.4
		Strattice	144	42.6	28.2	6.7	16.6	66.7	18.8	6.3	1.4	0.0	2.1	1.4	1.4
Lewis et al[21]	Retrospective review	AlloDerm	93	51.9	27.0	1.7	12.0	NA	NA	41.9	8.6	NA	11.8	5.4	7.5
		AlloDerm RTU	74	55.3	27.3	2.2	18.0	NA	NA	27.0	2.7	NA	10.8	2.7	8.1
Venturi et al[17]	Prospective cohort	AlloMax	65	49.3	25.6	NA	NA	NA	0.0	4.6	1.5	0.0	1.5	3.0	NA
Weichman et al[19]	Prospective cohort	AlloDerm	90	49	26.6	NA	6.7	40.0	14.4	NA	4.4	1.1	20.0	13.3	6.6
		AlloDerm RTU	105	50	24.9	NA	5.7	46.7	5.8	NA	1.0	0.0	8.5	10.4	1.9
Yuen et al[20]	Retrospective review	AlloDerm	96	50.5	30.3	8.0	NA	39.0	28.0	NA	18.8	NA	12.5	NA	7.3
		AlloDerm RTU	100	51.2	30.2	6.0	NA	44.0	14.0	NA	22.0	NA	21.0	NA	6.0

BMI, body mass index; NA, data not available; Pts, patients (study did not list the number of reconstructions); and XRT, radiation therapy.

influence of surgeon learning curve, as the aseptic Alloderm was used earlier in the surgeon's experience. Lewis et al[21] also recently reported on their comparison of aseptic AlloDerm with sterile Alloderm RTU and showed that although infection rates were similar (11.8% vs 10.8%, respectively; $P = 1.000$), overall complication rates were lower with sterile Alloderm RTU compared with aseptic Alloderm (27.0%–41.9%, respectively; $P = 0.046$).[21]

ALTERNATIVES TO ADM IN IMPLANT-BASED BREAST RECONSTRUCTION

Manufacturers have begun to offer an increasing variety of ADM alternatives for use in breast reconstruction. Patients who are not candidates for human ADM for medical, ideological, or religious reasons now have several options to choose from. However, given that most products have been on the market for a relatively short period of time, there are limited outcome data on their effectiveness and safety in breast reconstruction. One such product that has received interest is the SERI Surgical Scaffold (Allergan, Inc, Irvine, Calif.), approved for use in the United States in 2009. SERI is a knitted, bioresorbable scaffold composed of silk-derived fibroin, which is indicated for soft-tissue reinforcement and general soft-tissue reconstruction.[44,45] Before packaging, SERI is washed and sterilized.[44,45] In an ovine model evaluating the use of SERI surgical scaffold for two-stage breast reconstruction, Gross et al[44] reported that SERI-incorporated tissue samples maintained at least 150% of native ovine fascial strength at all endpoints. Knitted polyglactin 910 (Vicryl; Ethicon, Inc., Somerville, N.J.) mesh has also been described as an alternative to ADM in direct-to-implant breast reconstruction after skin-sparing mastectomy because of its relatively inexpensive costs, ease of use, resistance to biofilm formation, and nonallergenic composition.[12]

Another alternative, the titanium-coated polypropylene mesh (TiLOOP Bra, pfm medical, Cologne, Germany) has been described for use in implant-based breast reconstruction.[46] Despite approval in Europe since 2008, there remain limited data regarding safety and outcomes.[46] As an autologous option, dermal sling-assisted breast reconstruction, also known as the Bostwick autoderm technique, has been reported as an alternative to ADM use.[47,48] In this procedure, the inferior pole mastectomy skin is deepithelialized and adjoined to the inferior border of the pectoralis major muscle to create a tension-free vascularized pocket.[47,48] The technique may be used in either one- or two-stage breast reconstruction patients who have excess lower pole skin after mastectomy.[48]

DISCUSSION

The use of ADM in single- and two-stage breast reconstruction remains popular because of its ease of use and improved TE/I control within the mastectomy pocket.[15,19,22–24] There have been several studies that have reported low morbidity with the use of ADM in breast reconstruction,[13,17,18,22] and there is a growing body of anecdotal evidence suggesting improved aesthetic outcomes in reconstruction patients.[13,25–27,29,30,49,50] However, plastic

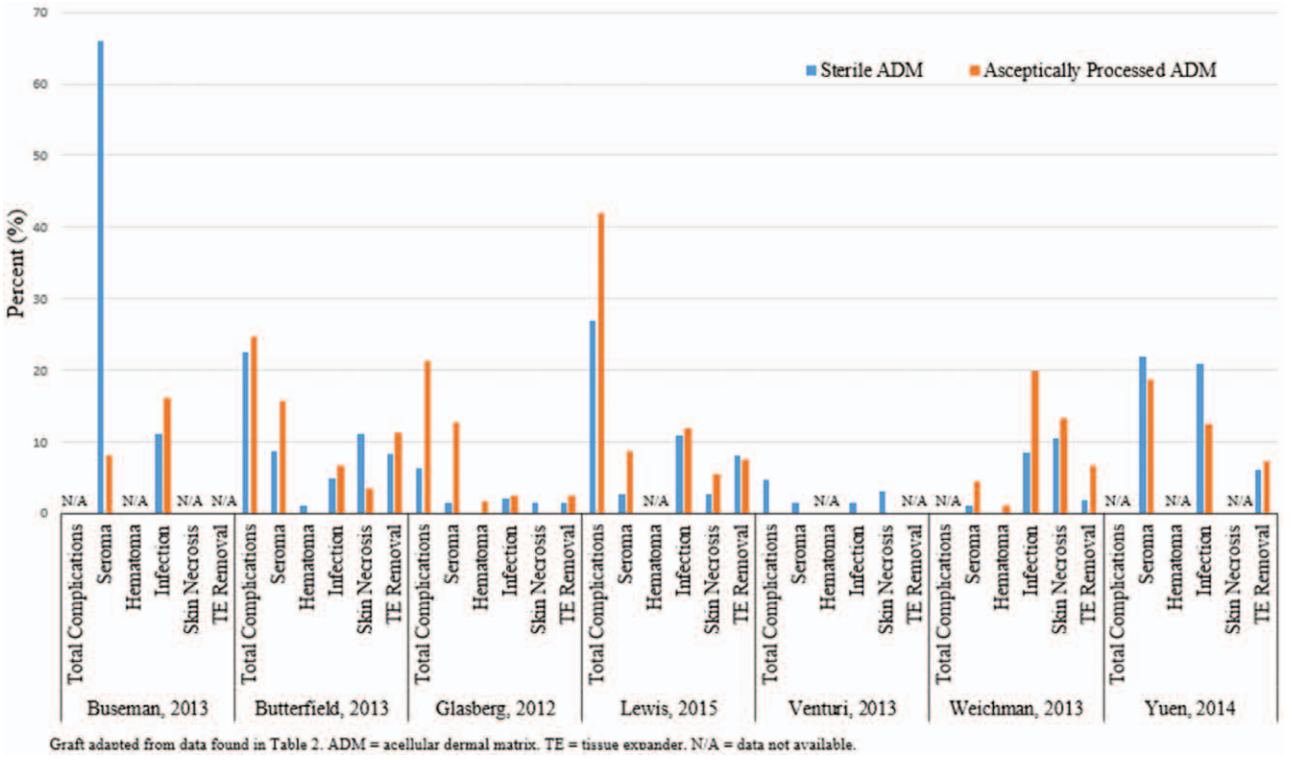

Fig. 4. Study outcomes comparing aseptically processed to sterile-processed acellular dermal matrix in breast reconstruction.

surgeons continue to weigh the advantages of ADM against a growing body of the literature reporting on increased morbidity with its use. Alongside the clear benefits made possible by ADM in breast reconstruction, complications attributed to its use have led some authors to advocate for caution and selective use of the material.[9,13] Numerous studies have reported on increased complication rates associated with ADM use in breast reconstruction,[9,26,51,52] with a majority of the studies focused on the earliest available ADM, Alloderm (LifeCell, Branchburg, N.J.).[9,14,24,26,49,52–55] Furthermore, several studies have attempted to isolate independent variables that may increase complication rates with ADM usage, such as elevated patient body mass index, higher patient age and axillary dissection,[52] and potential variables such as surgeon experience and technique.[15,26,56] Attempting to make sense of data from smaller, typically single-center studies, recent systematic reviews and meta-analyses have pooled complication data on ADM usage in implant-based breast reconstruction.

In a 2011 systematic review and meta-analysis, Hoppe et al[34] compared complication rates of AlloDerm-assisted two-stage breast reconstruction with traditional non-ADM–assisted implant/expander techniques after mastectomy.[34] Three of the included studies[22,27,53] reported no difference in the complication rate and 4 studies[9,26,51,52] reported an increased rate of complications between cohorts.[34] When compared with the non-ADM cohort, the ADM-assisted group reported a 2-fold increase in infection rates (odds ratio [OR], 2.33), a 3-fold increase in seroma formation (OR, 3.00), and a 2-fold increase in the TE/I explantation rate (OR, 2.41).[34] Similar complication rates were reported in a systematic review by Ho et al,[35] which focused on single-stage and two-stage breast reconstructions using ADM. A systematic review by Sbitany et al[57] in 2011 found higher seroma rates to be the only significant complication difference between ADM and non-ADM cohorts (8.4% vs 4.3%; $p = 0.03$). A meta-analysis by Kim et al[16] in 2012 estimated complication rates in TE/I reconstructions using ADM. Nineteen studies reporting ADM use (4 of which reported on single-stage reconstruction with ADM) and 35 studies reporting submuscular techniques without ADM were used to estimate complication rates. Complication rates were higher with ADM use versus no ADM with specific complications including flap necrosis (6.9% vs 4.9%), infection (5.3% vs 4.7%), and seroma (4.8% vs 3.5%).[16]

One potential explanation for the reported increases in infection rates with ADM usage in breast reconstruction is that the ADM may serve as a nidus for bacteria. Some investigators have proposed a tiered sterility classification that is product specific with regard to product vulnerability to damage from sterilization and level of risk to the patient.[41] For example, items that can withstand high heat (such as surgical instruments) would undergo high-level sterilization to an SAL of 10^{-6}, whereas heat-sensitive products (such as biologics) would undergo low-level sterilization to a SAL of 10^{-3} and still be considered "sterile" for their intended use. Aseptically processed items generally do not have an associated SAL because they do not undergo a validated terminal sterilization process (Table 1).

Although the advent of terminally sterilized ADM has been marketed as a potentially "cleaner" alternative to the aseptically processed biologics, the current

data comparing the two have been largely inconclusive because of study design flaws including unmatched cohorts, underpowered populations, and confounding variables ultimately resulting in studies with a low level-of-evidence. One of the highest quality studies to date that evaluated use of ADMs in implant breast reconstruction, the BREASTrial, recently reported on outcomes from the time of mastectomy and tissue expander placement to completion of the reconstruction process.[58] This was a large prospective randomized trial comparing outcomes of immediate-staged tissue expander breast reconstruction using either AlloDerm or DermaMatrix.[58] One hundred twenty-eight patients were randomly assigned to either of the ADM groups, and the impact of obesity, chemotherapy, and radiation was assessed in regard to complications and biointegration of the ADMs. Similar overall complication rates were observed between the AlloDerm and DermaMatrix groups (33.6% vs 38.8%, respectively). No differences in complications were noted on regression. In both groups, obesity contributed to poor matrix biointegration, longer drain times, and increased complication rates. As evidence of the rapidly evolving nature of ADMs, the study was initiated at a time that preceded the introduction of sterile-processed Alloderm and as such both ADMs in the study are aseptically processed. Similar well-designed prospective studies are needed to help tackle questions on the effect of ADM processing on outcomes.

CONCLUSIONS

Acellular dermal matrices have made significant contributions to the evolution of single- and two-stage implant breast reconstruction after mastectomy. Careful patient selection continues to be critical in efforts made to optimize outcomes of breast reconstruction with acellular dermal matrices. The impact of ADM processing techniques on postoperative morbidity in implant-based breast reconstruction is unclear at this point, highlighting the need for well-designed, multicenter, randomized controlled studies on this subject.

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