

Human Acellular Dermal Matrix (Epiflex®) in Immediate Implant-Based Breast Reconstruction after Skin- and Nipple-Sparing Mastectomy and Treatment of Capsular Fibrosis: Results of a Multicenter, Prospective, Observational NOGGO-AWOGyn Study

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Keywords

Breast reconstruction · Human acellular dermal matrix · Complications · Capsular fibrosis

Abstract

Background: Over the last decades, the number of acellular dermal matrix (ADM)-assisted implant-based breast reconstructions (IBBR) has substantially increased. However, there is still a lack of prospective data on complication rates. **Methods:** We performed a non-interventional, multicenter, prospective cohort study to evaluate complication rates of a human ADM in patients undergoing an IBBR after skin- and nipple-sparing mastectomies. Patients with primary reconstruction (cohort A) and patients undergoing a secondary reconstruction after capsular fibrosis (cohort B) using the human ADM Epiflex® (DIZG gGmbH, Berlin, Germany) were enrolled in this study. Patients were followed-up for 12

months after surgery. **Results:** Eighty-four eligible patients were included in this study of whom 28 women underwent a bilateral breast reconstruction, leading to 112 human ADM-assisted reconstructions in total (cohort A: 73, cohort B: 39). In 33.0% of the reconstructed breasts at least one of the complications of primary interest occurred, including implant loss 7.1%, seroma 15.2%; infection 5.4%, rash 8.0%, and Baker grade III/IV capsular fibrosis 2.7%, with no statistically significant differences between the cohorts. Previous radiation therapy was significantly associated with occurrence of any postoperative complication (OR 20.41; *p* value 0.027). **Conclusion:** The rates of most complications were comparable to the rates reported for other ADMs with relatively low rates of capsular fibrosis and infections. The rate of seroma was increased in our study. Prior radiation therapy increased the risk of any postoperative complications. Therefore, the use of ADM in these patients should be considered carefully.

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Background

The number of immediate breast reconstructions after skin- and nipple-sparing mastectomies has increased substantially in the last years [1]. This might be explained by several reasons including an increasing incidence of breast cancer and a rising number of patients surviving breast cancer [2]. The improved oncological safety and quality of silicone implants as well as the increase of prophylactic mastectomies might represent further driving factors [1, 3–6]. Implant based breast reconstructions (IBBR) account for the vast majority of breast reconstructions worldwide [2, 7]. In recent years, the use of matrices in implant-based reconstruction gained popularity [2, 8]. Reported advantages of matrices in breast reconstruction include the reduction of capsular contraction, improved aesthetic outcomes, better control of the inframammary and lateral fold, reduced surgery times, improved expansion of the lower pole, and a reduction of postoperative pain [8–12]. However, also increased risks of seroma, skin necrosis, infections, and loss of implants associated with acellular dermal matrix (ADM)-assisted breast reconstructions were reported in previous studies [8, 11, 13].

Although several studies including systematic reviews and meta-analyses have been published in the past, there is still no clear evidence of the rate of complications associated with ADM-assisted breast reconstructions. Reported complication rates of ADM-assisted IBBR are contradictory, ranging from <5 to >50% [2, 14] with the majority of previous studies being retrospective analyses. The heterogeneous data on complication rates also impacts the discussion on the cost-effectiveness of ADM-assisted IBBR. In summary, although there is evidence that ADMs improve the results of implant-based reconstructions, current data on complication rates are heterogeneous, and prospective data on complication rates are rare. Most data on human ADMs are based on Alloderm® (Lifecell Inc., Branchburg, NJ, USA) and FlexHD® (Musculoskeletal Transplant Foundation, Edison, NJ, USA) which are not available in Germany. The aim of the present study was to prospectively evaluate the complication rates of a human ADM in patients undergoing immediate breast reconstruction after skin- and nipple-sparing mastectomies.

Material and Methods

Study Design

We conducted a non-interventional, multicenter, prospective cohort study at 11 sites with experience in ADM-assisted breast reconstructions in Germany (German Clinical Trials Register-ID DRKS00007587). The study was approved by Ethics Committees at all participating sites. Patients were followed up for 1 year. Study visits were scheduled 1, 7 and 30 days, and 3, 6 and 12 months after surgery. Baseline data including demographics, medical history, and potential predictors of complications were collected prior to surgery.

The objective of the study was to evaluate complication rates in patients undergoing a breast reconstruction with the human ADM Epiflex® (German Institute for Cell and Tissue Replacement (DIZG) gGmbH, Berlin, Germany). The primary endpoint of the study was defined as loss of implant. Secondary endpoints of interest included seroma, infection, rash (red breast syndrome), capsular fibrosis (any grade), and Baker grade III/IV capsular fibrosis. In this non-interventional study, physicians were asked to document all complications, independent of clinical relevance and severity. Complication rates were evaluated in all patients enrolled in this study and separately in patients undergoing a primary reconstruction and patients undergoing a secondary reconstructing after capsular fibrosis. The study was unrestrictedly funded by Berliner Krebsgesellschaft e.V., NOGGO e.V., AWOGyn e.V., Förderverein Berliner Brustzentren e.V., and the German Institute for Cell and Tissue Replacement (DIZG).

Study Population

Physicians were asked to consecutively enroll women undergoing a human ADM-assisted immediate submuscular IBBR after skin- and nipple-sparing mastectomy, ≥18 years of age who provided written informed consent. Patients were enrolled into 2 cohorts: cohort A – patients without prior reconstruction and cohort B – patients undergoing a secondary submuscular implant-based reconstruction after implant-caused capsular fibrosis. Patients with an autoimmune disease, known contraindication against ADM-assisted or plastic reconstructive breast surgery, previous radiotherapy (only in cohort A) and pregnant or breast-feeding women were not eligible for inclusion.

Materials

All patients were treated with the human ADM Epiflex® (German Institute for Cell and Tissue Replacement [DIZG] gGmbH, Berlin, Germany). Epiflex® is produced from skin of serologically screened donors by validated procedures including decellularization, sterilization, and preservation of the tissue. Epiflex® is sterilized using a validated, GMP-conformable process and approved as a medicinal product under §21 of the German Medicinal Products Act (license number: 3003749.00.00).

Surgery

In our study, IBBR was performed after skin- and nipple-sparing mastectomy from breast surgeons as a one-step breast surgery and reconstruction procedure. To ensure better comparability of the results, a uniform surgery procedure has been prescribed corresponding to the manufacturer's technical information, and training courses were offered for all participating sites. Only sites with experience in the use of Epiflex® were eligible for participation in this study. All patients enrolled in this study underwent a submuscular reconstruction. Antibiosis was performed perioperatively until drain removal.

Statistical Analysis

Patients fulfilling all eligibility criteria were included in the analyses. Descriptive analyses of all parameters were performed providing absolute frequencies and proportions for categorical variables and mean, SD, and range for continuous variables. Complication rates are reported per breast for the overall study population and separately for patients undergoing a primary breast reconstruction and patients undergoing a secondary breast reconstruction after capsular fibrosis. Complication rates between the study cohorts were exploratory compared to each other. Comparisons between the study cohorts were made using the χ^2 test for categorical variables and parametric Student *t* test or non-parametric Mann-Whitney U test as appropriate for con-

Table 1. Patient characteristics

Patient characteristic	Total (n = 84)	Cohort A (n = 53)	Cohort B (n = 31)	p value
Age, years				
Mean (SD)	44.5 (11.9)	41.4 (9.9)	49.8 (13.2)	0.001
Range	22–75	22–62	27–75	
Body mass index, kg/m ²				
Mean (SD)	22.1 (2.8)	22.0 (3.0)	22.2 (2.5)	0.403
Range	17.8–32.5	17.8–32.5	17.9–27.5	
Smokers, n (%)	18 (21.4)	9 (17.0)	9 (29.0)	0.430
Comorbidities, n (%)				
Hypothyroidism	9 (10.7)	3 (5.7)	6 (19.4)	0.050
Hypertension	10 (11.9)	3 (5.7)	7 (22.6)	0.021
Depression	3 (3.6)	0 (0.0)	3 (9.7)	0.021
Prior therapy, n (%)				
Radiation therapy	7 (8.3)	0 (0.0)	7 (22.6)	0.000
Neoadjuvant chemotherapy	21 (25.0)	14 (26.4)	7 (22.6)	0.695
Endocrine therapy	23 (27.4)	8 (15.1)	15 (48.4)	0.001
Indication, n (%)				
Prophylactic ^a	37 (44.0)	29 (54.7)	8 (25.8)	0.021
Invasive breast cancer	48 (57.1)	34 (64.2)	14 (45.2)	0.090
Precancerosis/DCIS	16 (19.0)	10 (18.9)	6 (19.4)	0.956

^a Including confirmed BRCA mutations and breast cancer in the family history.

Table 2. Surgical details per patient

Surgery detail	Total (n = 84)	Cohort A ^a (n = 53)	Cohort B (n = 31)
Site of reconstruction, n (%)			
Unilateral	56 (66.7)	33 (62.3)	23 (74.2)
Bilateral	28 (33.3)	20 (37.7)	8 (25.8)
Surgery time, min			
Unilateral, mean (SD)	130.7 (57.2)	147.6 (62.7)	106.4 (37.5)
Range	45–325	45–325	57–210
Bilateral, mean (SD)	189.4 (47.6)	202.4 (38.5)	157.0 (55.1)
Range	80–280	128–280	80–263
Cutting to shape of Epiflex®, n (%)	49 (58.3)	29 (54.7)	20 (64.5)
Reported blood loss during surgery, n (%)	59 (70.2)	37 (69.8)	22 (71.0)
Amount, mean (SD), mL ^b	146.3 (111.2)	172.9 (128.9)	104.1 (55.2)
Range, mL	20–600	20–600	20–200
Complications during surgery, n (%)	2 (2.4)	2 (3.8)	0 (0.0)

^a Including the time for mastectomy in cohort A. ^b Three outliers (>1.5 × interquartile range) were identified in cohort A.

tinuous variables. To account for potential dependency in case of bilateral reconstructions, multivariable logistic regression was conducted per women to evaluate risk factors for occurrence of any complication (loss of implant, seroma, infections, rash, Baker grade III/IV capsular fibrosis). In order to increase the power of the model, the multivariable logistic regression model was based on all patients enrolled in this study adjusting for the study cohort.

A 2-sided *p* value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics 25 (IBM, USA).

Results

Patient Population

Eighty-four eligible patients were enrolled in the study between January 2015 and September 2018. Patient characteristics are reported in Table 1. Mean follow-up time was 9.7 months (SD 3.9). Mean age was 44.5 years (11.9). Patients in cohort A were significantly younger compared to patients in cohort B (41.4 [SD 9.9] and 49.8 [SD 13.2], respectively). 25.0% of the patients had prior neoadjuvant

Table 3. Occurrence of complications per reconstructed breast stratified by study cohort

Complication	Total (n = 112)	Cohort A (n = 73)	Cohort B (n = 39)	p value
Loss of implant	8 (7.1)	7 (9.6)	1 (2.6)	0.474
Seroma	17 (15.2)	11 (15.1)	6 (15.4)	0.724
Infection	6 (5.4)	5 (6.8)	1 (2.6)	0.648
Rash	9 (8.0)	4 (5.5)	5 (12.8)	0.111
Baker grade III/IV capsular fibrosis	3 (2.7)	1 (1.4)	2 (5.1)	0.277

chemotherapy, and 27.4% had prior endocrine therapy with a higher proportion in cohort B (48.4 vs. 15.1% in cohort A). The indication for the mastectomy was prophylactic in 44.0% of the patients, 57.1% had a histologically confirmed invasive breast cancer, and 19.0% reported a precancerous like ductal carcinoma in situ.

Surgery

Surgical details are presented in Table 2. Of the 84 women, 28 women underwent immediate bilateral sub-muscular IBBR using human ADM, leading to 112 ADM-assisted reconstructions in total. Of the 112 breasts, 73 were encountered in cohort A and 39 in cohort B. Mean surgery time for unilateral reconstructions was 130.7 min (SD 57.2) and 189.4 min (SD 47.6) for bilateral reconstructions. The surgery times were longer in the primary reconstruction situation (cohort A), which comprised the time for the mastectomy, compared to the secondary reconstruction (cohort B). The ADMs were adjusted in shape in 58.3% of all reconstructions. Problems during surgery were reported in 2 cases (2.4%): difficulties in control of intraoperative bleedings in 1 case and increased difficulty due to a thin skin mantle in the other.

Postoperative Complications

In 33.0% of the reconstructed breasts at least one of the complications of interest occurred. Postoperative complications are reported in Table 3.

Loss of Implant

During follow-up, 8 implants (7.1%) had to be removed, 7 (9.6%) in cohort A and 1 (2.6%) in cohort B. In 2 patients with bilateral reconstruction, both implants had to be removed.

Five of these reconstruction failures were reported at the visit 30 days after surgery, 2 reconstruction failures were reported 6 months after surgery, and 1 was reported 1 year after surgery.

In 1 patient, seroma was reported at time of reimplantation. In 1 patient, the implant loss coincided with seroma, infection, skin necrosis, and rash. In 1 case of

bilateral revision, necrosis of one breast and severe swelling of the other breast were reported. The other bilateral explantation was reported to be due to seroma and an impaired wound healing. In 1 case, jumping breast was diagnosed which resulted in removal of the implant. For one explantation, no further complication was reported.

Seroma

Seroma was the most common complication, occurring in 17 (15.2%) of the 112 reconstructed breasts with an incidence of 11 (15.1%) in cohort A and 6 (15.4%) in cohort B. In 1 patient with bilateral breast reconstruction, seroma occurred in both reconstructed breasts. One case was reported immediately after surgery, 7 cases occurred until 1 week after surgery, 7 occurred 1 month after surgery, 1 occurred 3 months after surgery, and 1 six months after surgery. In 3 cases, where occurrence of seroma was reported, the implant was removed.

Infections

Infections were encountered in 6 breasts (5.4%), 5 (6.8%) in cohort A and 1 (2.6%) in cohort B. Two infections were reported 1 week after surgery, 4 were reported 1 month after surgery. In 1 of the bilateral reconstructions, both breasts were infected during follow-up. In these breasts, the infections coincided with occurrence of seroma, skin necrosis, and rash. In one of the breasts, the implant was removed. In 1 case, the reported infection coincided with the occurrence of seroma. One infection coincided with the occurrence of seroma and wound dehiscence. In 2 cases, no further complication was reported.

Rash

Occurrence of rash was reported in 9 breasts (8.0%), 4 (5.5%) in cohort A and 5 (12.8%) in cohort B. Two cases were reported immediately after surgery, 5 occurred 1 week after surgery, and 2 until 1 months after surgery.

Capsular Fibrosis

Capsular fibrosis was reported in 12 breasts (10.7%). However, only 3 cases (2.7%) were classified as Baker Grade III or IV with an incidence of 1 (1.4%) in cohort A and 2 (5.1%) in cohort B. Two cases were first reported 3 months after surgery and 1 year after surgery.

Risk Factors for Postoperative Complications

Results from multivariate logistic regression for risk factors of complications are reported in Table 4. Previous radiation therapy (p value 0.027, odds ratio [OR] 20.41) was associated with the occurrence of any complication including loss of implant, seroma, infections, rash, any capsular fibrosis. Of the 7 patients with previous radia-

Table 4. Multivariate logistic regression analyses to evaluate risk factors for any postoperative complication

Risk factor	Odds ratio	95% CI	<i>p</i> value
Age, years	1.02	0.95–1.09	0.672
BMI	0.85	0.68–1.06	0.151
Smoker	1.31	0.42–4.02	0.641
Hypertension	0.70	0.09–5.65	0.740
Hypothyroidism	0.82	0.12–5.43	0.838
Depression	11.79	0.39–356.88	0.156
Neoadjuvant chemotherapy	2.05	0.44–9.48	0.358
Endocrine therapy	0.62	0.13–2.85	0.539
Radiation therapy	20.41	1.42–294.14	0.027
Invasive breast cancer	1.97	0.44–8.88	0.376
Precancerosis	0.23	0.03–1.67	0.147
Duration of surgery	0.99	0.98–1.01	0.245
Cutting to shape of Epiflex®	0.96	0.74–1.25	0.763
Bilateral surgery	0.60	0.11–3.22	0.547
Blood loss during surgery	2.25	0.65–7.72	0.199
Revision surgery	0.61	0.12–3.13	0.555

Complications include loss of implant, seroma, infections, rash and Baker grade III/IV capsular fibrosis. CI, confidence interval; BMI, body mass index.

tion therapy, 6 patients (85.7%) had at least one of the following complications. Loss of implant was reported in 1 (14.3%) patient, seroma in 2 (28.6%) patients, rash in 3 (42.9%) patients, and capsular fibrosis in 2 (28.6%) patients. No infections were reported.

Discussion

With the increased use of ADMs in breast reconstructions, several studies on complication rates of ADMs were conducted. However, complication rates vary widely between studies with the majority being retrospective studies. This is the first prospective study to evaluate the safety of human ADM-assisted immediate breast reconstructions after skin- and nipple-sparing mastectomy in patients with and without prior breast reconstruction. The mean follow-up time in the present study was 9.7 months with no significant differences between the study cohorts.

One of the main advantages of ADMs is the reduced rate of capsular fibrosis [9, 11, 15], which is one of the most common complications of IBBR [9]. In a recently published systematic review, the rate of capsular contracture after prepectoral breast reconstruction was reduced to 2.3% in patients with ADM compared to 12.4% in patients without ADM [16]. In our study, we found an overall Baker grade III or IV capsular fibrosis rate of 2.7%, which is in line with these findings. The incidence

of capsular fibrosis was higher in cohort B (5.1%) compared to cohort A (1.4%). This might be due to the inclusion of patients with prior radiation therapy and reconstruction surgery due to prior capsular fibrosis in cohort B, whereas prior radiation therapy was an exclusion criterion in cohort A. Both cases with Baker grade III/IV capsular fibrosis in cohort B had a prior radiation therapy. Although postoperative radiation therapy was not assessed systematically in this study, it was reported that the capsular fibrosis in the affected patient in cohort A, occurred after postoperative radiation treatment during follow-up. Radiation therapy was identified as risk factor for capsular contracture in breast reconstruction in previous studies [9, 17]. In our study, previous radiation therapy was identified as a risk factor for occurrence of any complication, while it could not be identified as an independent risk factor for capsular fibrosis solely, which might be explained by the small sample size. Notably, patients with previous radiotherapy were only enrolled in cohort B, that is, in a secondary reconstruction situation. Receiving a radiotherapy prior to a skin- and nipple-sparing mastectomy is unlikely in clinical practice.

A large retrospective chart review with a mean follow-up of 4.7 years by Salzberg et al. [9] showed that capsular contracture in ADM-assisted breast reconstructions is an early event, with all events occurring within 2 years after surgery in their study. In our study, the median follow-up time was 9.7 months; thus, we might have missed the occurrence of some capsular fibroses. Importantly, in our study using implant-based reconstruction with human ADM, it was possible to achieve results without capsular fibrosis in patients with implant related capsular contraction before, indicating that not in every patient with capsular contracture, an autologous reconstruction is required. However, due to our short follow-up period, further studies with a longer follow-up period are needed to confirm this as capsular fibrosis might have occurred later.

In a meta-analysis from Hallberg et al. [8], the overall incidence of implant loss in the included studies ranged from 0 to 17%. In a systematic review, the pooled explanation rate was slightly lower with 4.1% [18]. Other meta-analysis reported comparable rates of reconstruction failures [11, 19]. Sorkin et al. [20] found an explanation rate of 9.2% in a large prospective cohort study including 655 patients undergoing ADM-assisted breast reconstructions, with similar risks as compared to patients without ADMs. In our study, 7.1% of reconstructions failed.

The most common postoperative complication in our study was seroma with an incidence of 15.2%. It was reported previously that the use of ADM increases the rate of seroma as compared to breast reconstructions without ADMs [13, 15] with rates spread widely across previous

studies. The high incidence of seroma formation associated with use of ADM is hypothesized to be caused by an immunological response towards the ADM [15, 21], especially prior to revascularization of the ADM [15]. In line with this argumentation, seroma formation was an early event in our study: 15 out of 17 reported seroma occurring within the first month after surgery. Skovsted Yde et al. [22] reported rates for Alloderm[®] varying from 2.1 to 18% in previous studies. In a large retrospective analysis, Chun et al. [13] revealed a rate of seroma of 14.1% in patients undergoing an ADM-assisted immediate breast reconstruction. The pooled rate of seroma in a meta-analysis from Kim et al. [19] was 4.8%, whilst Smith et al. [23] reported a rate of 8.3% in breast reconstructions with human ADMs. In our study, the rates were higher compared to the findings from other studies. Notably, the comparability of incidence rates is limited by differing outcome assessments. Importantly, in the current study we documented all seromas, including those that did not require any intervention. Postoperative ultrasounds were routinely performed in our study sites by breast surgeons and may explain the high rate of ultrasound detected yet clinically non-relevant seroma.

In a meta-analysis, the risk of infections was significantly increased in patients undergoing a breast reconstruction with human ADMs as compared to patients undergoing submuscular reconstruction with infection rates of 7.2 and 5.9%, respectively [23]. In our study, the rate of infections was slightly lower (5.4%).

The rate of rash in the present study was comparable to the rate reported by Negenborn et al. [14].

Our study identified previous radiation therapy as a predictor of any postoperative complication, which was also identified as a risk factor in other studies [9, 17, 24]. In contrast to our study, smoking status [24–26], high BMI (≥ 30 kg/m²) [26, 27], and previous chemotherapy [14, 24, 26] were shown to be predictors of complications in other studies. Breast size and weight of implant, which were described to be among the most predictive factors for complications previously [14, 25, 26], were not assessed in the present study. Due to the relatively small number of patients, results from the multivariate regression analysis should be interpreted with caution and only give an indication for risk factors.

In our study, the complication rates were not statistically different in patients with a primary breast reconstruction compared to patients undergoing a revision surgery after capsular fibrosis, indicating that Epiflex[®] is safe to use in primary breast reconstruction as well as in revision surgery after capsular fibrosis. However, due to our short follow-up period and relatively low sample sizes in the cohorts, this needs to be confirmed in further studies with larger sample sizes and longer follow-ups. Despite this limitation, this is the first study to prospec-

tively evaluate the complications rates in primary breast reconstruction and secondary breast reconstruction after capsular fibrosis using a human ADM. In a retrospective study with a median follow-up of 3 years, Paprottka et al. [28] found the use of human ADMs to be associated with the lowest risk of complications compared to porcine ADMs and bovine ADMs.

Conclusion

In our study, most complication rates for the use of the human ADM Epiflex[®] in immediate IBBR and for treatment of capsular fibrosis were comparable to the rates reported for other ADMs, with relatively low rates of capsular fibrosis and infections. Only the rate of seroma was higher compared to previous studies. The complication rates were not statistically different in patients with a primary breast reconstruction compared to patients undergoing a revision surgery after capsular fibrosis. The risk of any postoperative complications was increased in patients with prior radiation therapy. Therefore, the use of ADM in these patients should be considered carefully.

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Statement of Ethics

The study was approved by Ethics Committees at all participating sites (Ethics Committee of the Charité – Universitätsmedizin Berlin, Landesärztekammer Baden-Württemberg, Otto-von Guericke-Universität an der Medizinischen Fakultät und am Universitätsklinikum Magdeburg, Technische Universität München, Medizinische Hochschule Hannover, Ärztekammer Westfalen-Lippe). Written informed consent was obtained from all study participants in order to participate in the study.

Conflict of Interest Statement

Prof. MD Andree Faridi is a consultant of pfm Köln and received speaking fees from pfm Köln and DIZG Berlin. MD Stefan Paepke received fees from pfm, tapmed, novusscientific and DIZG. Prof. MD Sherko Kümmel received consulting fees from F. Hoffmann-La Roche Ltd, Genomic Health, Novartis, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, Somatex, MSD, Pfizer, Puma Biotechnology, PFM Medical, Lilly. All other authors have no conflicts of interest to declare.

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Author Contributions

L.B.: performed the data analyses and wrote the manuscript with input from all authors. A.F., M.K., S.K., and J.-U.B.: contributed to the study design and writing of the study protocol. A.F., C.N., S.P., C.M., H.J.S., C.G.-S., L.B., M.M.K., and J.-U.B.: contributed to data collection and data interpretation.

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