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Difficult-To-Treat Periprosthetic Hip Infection: Outcomes of Debridment

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Abstract

Purpose of the study — to compare management efficiency for difficult-to-treat periprosthetic hip infection (PJI) during resection arthroplasty with grafting by vastus lateralis pedicle island flap in comparison with insertion of an antimicrobial-loaded cement spacer. ***Material and Methods.*** 132 patients were included into the retrospective study who underwent treatment from 2012 until 2018 including removal of orthopaedic implant, radical surgical debridement of infection focus, resection arthroplasty with grafting by vastus lateralis pedicle island muscle flap (PMF group — 57 patients) or insertion of antibacterial-loaded cement spacer (AMS group — 75 patients). The authors examined medical histories, nature of infection process, infection agent type, laboratory data in respect of systemic inflammation, size of bone defects, follow up status and remission of PJI in the late period. ***Results.*** 89.4% of patients (n = 51) who underwent grafting by vastus lateralis pedicle island flap had a history of 3 and more prior surgical procedures in the same area. At the same time the share of such patients in the spacer group was only 38.6% (n = 29) (p<0.0001) while the share of patients with two and more recurrences was 78.9% (n = 45) and 25.3% (n = 19), respectively (p<0.0001). No significant variances were observed between the groups in respect of type composition of PJI microbial infection agents. The infection in a vast majority of patients in both groups was caused by microbial association: 77.2% and 72.0% in PMF and AMS groups, respectively. In the early postoperative period secondary revision of surgical site was performed in 35% and 28% of cases in PMF group (n = 20) and AMS group (n = 21), respectively, including due to recurrent infection in 15.8% and 28% of cases, respectively. Stable remission of difficult-to-treat PJI in PMF group was 96.5% and 45.3% in AMS group. ***Conclusion.*** Despite some cases that required secondary revisions in early postoperative period the resection arthroplasty in combination with pedicle muscle flap can be considered a surgery of choice for management of recurrent difficult-to-treat PJI with feasible re-implantation of prosthesis against the stable remission of infection.

Keywords: difficult-to-treat periprosthetic infection, muscle flap, resection arthroplasty, stable remission of infection, antimicrobial-loaded cement spacer.

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Introduction

Surgical tactics for treatment of periprosthetic joint infection (PJI) is constantly improving and actively discussed in scientific publications, all current clinical algorithms for the mentioned pathology take into account the length and pattern of infectious process surrounding the prosthesis, type of agent and its resistant to antibiotics as well as status of the patient [1]. Recently key emphasis is placed on the polyresistant agents inducing PJI that reduce the efficiency of sanation surgeries and etiotropic antibacterial therapy which often results in multiple recurrence of infection [2, 3, 4]. This naturally led to the appearance in the literature of a new term "difficult-to-treat" describing intractable periprosthetic infection (DTT PJI) caused by difficult-to-eradicate (DTE) agents resistant to antibiotics active against microbial biofilms. Rifampicin-resistant staphylococcus strains, ciprofloxacin-resistant strains of gram-negative bacteria and fungi of *Candida genus* [5].

It's known that identification of gram-negative strains resistant to ciprofloxacin and producing beta-lactamase of the extended spectrum reduces the efficiency of managing early PJI after sanation and preserving the prosthesis 79 to 53% and 42,8%, respectively, during two years follow up [6]. Two stage treatment with antimicrobial spacers (AMS) as well demonstrates a low efficiency: from 28 to 50-52% in case of infection induced by gram-negative bacteria and microbial associations [5, 7, 8, 9].

It should be noted that until now there is no integral view on the treatment tactics for patients with multiple recurrent PJI caused by such complex agents. One of the most efficient method of PJI treatment after many sanation surgeries is the "desperate surgery", namely, resection arthroplasty of the hip joint known as Girdlestone procedure. Published studies demonstrate considerable variations in efficiency of infection management: from 73 to 100% [10], at the same recurrent infection in patients is often observed along with formation of chronic not-healing wounds with joint cavity being the floor of the wound [11]. In cases of combination of mentioned procedure with vastus lateralis pedicle island muscle flap the treatment efficiency increases and the rate of late PJI recurrence amounts to 5,9–10% [12, 13, 14]. However, the conducted analysis of scientific literature did not yield publications dedicated to treatment of patients with DTT hip PJI caused by DTE agents using resection hip arthroplasty in combination with grafting by pedicle island muscle flap (PMF) and exactly this defined the purpose of the present study.

Purpose of the study — to compare efficiency of management for difficult-to-treat periprosthetic hip joint infection (PJI) during resection arthroplasty with grafting by vastus lateralis pedicle island flap in comparison with insertion of an antimicrobial-loaded cement spacer.

Material and methods

Study design — single center retrospective study for the period from 2012 until 2018.

Inclusion criteria: chronic DTT PJI caused by DTE agents: rifampicin-resistant staphylococcus strains, ciprofloxacin-resistant strains gram-negative bacteria, fungi of Candida genus.

Exclusion criteria: sepsis at the moment of admission to hospital.

Overall, 132 patients were included into the study that were divided into groups depending on type of surgery. The first group of grafting by pedicle island muscle flap (PMF) included 57 patients who underwent removal of prosthesis components, radical debridement of infection focus, resection arthroplasty and transfer of vastus lateralis pedicle island muscle flap according to patented grafting technique (patent of Russian Federation 2 299 031 — grafting by pedicle island muscle flap after radical debridement of osteomyelitis nidus in the acetabulum).

Second group included 75 patients who underwent removal of implants, radical surgical debridement of infection focus and insertion of antimicrobial-loaded cement spacer (AMS).

Mean age of patients in PMF group was 59 years at the moment of surgery (IQR 52-67), men constituted 58% (n = 33), women — 42% (n = 24). Left hip joint was affected in 54% (n = 31), right joint — in 46% (n = 26). Mean age of patients in AMS group was 62 years (IQR 53-70), men constituted 48% (n = 36), women — 52% (n = 39). Left hip joint was affected in 45% (n = 34), right joint — in 55% (n = 41).

The share of patients with infection remission in one year and more after sanation surgery was taken as criteria of treatment efficiency for PMF group, and for AMS group — share of patients who successfully underwent second stage of two-stage procedure — reimplantation of hip joint prosthesis. Besides, for both groups the authors calculated the share of patients who required secondary revision in early postoperative period (30 days after surgery) due to hematoma in the area of intervention and/or persistent wound discharge for over 7 days and other manifestations of recurrent PJI.

Medical records and data of the local PJI register were used to examine medical history (infection agent, number of surgeries, number of prior PJI recurrences), type of pathogen, laboratory tests (total protein, hemoglobin, WBC count, ESR, CRP, fibrinogen) at admission, time of surgery, blood loss value, dimensions of defects in femur and acetabulum. Late outcomes (PJI remission) were evaluated at control examination of the patient.

Dimensions of defects in femur and acetabulum were assessed as small or large considering anatomical and x-ray landmarks and need for use of revision prosthesis for hip replacement in the future. Femur defects were considered small when bone loss was visualized in the area of femur physis with preserving of more than 4 cm of intact bone or a segmental defect of proximal femur. Femur defects were classified as large one when there was a deficit of cancellous and cortical diaphyseal bone with less than 4 cm of intact bone or a segmental defect of proximal femur. In such cases further hip arthroplasty is possible only by revision implants.

Acetabular defects were considered small with damage of the roof and acetabular component displacement (roentgenological data) up to the level not above 3 cm over the superior border of obturator foramen with probable destruction of anterior column but with preserved posterior column and minimal defect of acetabular floor with maintained bearing function for further joint arthroplasty. With roof destruction and acetabular displacement over 3 cm over the above border as well as with loss of bearing ability of posterior column and significant defect of acetabular floor the defects were classified as large and requiring support implants for hip joint arthroplasty. Combination of small femur and acetabular defects were classified as small hip joint defect, combination of large defects — to hip joint large defect. In case of a combination of small and large defects — the defect of hip joint bones was considered irregular.

From the date of surgery all patients received intravenous combined empiric or etiotropic antibacterial therapy with respect for obtained results of preoperative bacteriological tests of articular fluid and/or results of previous hospital stay. After obtaining results of testing the intraoperative biopsy samples the authors corrected antibacterial therapy towards oral antibiotics for 6-8 weeks.

Statistical analysis

The obtained data was registered in electronic spreadsheets, visualization of data structure and its analysis was performed by MS Office Excel, 2007 (Microsoft, USA), Statistica for Windows (version 10). Due to a small number of cases the median (Me)

was used as a measure of central tendency for studied characters, and lower and higher quartiles (25-75% IQR) as measures of dispersion. Matching of quantitative characters of the comparison groups was done by Mann Whitney U-test. c^2 was used for analysis of relative ratios. Relative risk (RR, 95% CI) and odds ratio (OR, 95% CI) were calculated to evaluate recurrence risk and chances for stable remission. Variances between the groups were considered statistically significant at $p<0,05$.

Results

Groups were comparable in terms of number of cases, gender and age. Duration of PJI in PMF group was significantly longer than in AMS group ($p<0,05$). It should be noted that majority of patients (89,4%; $n = 51$) who underwent muscle grafting had three and more surgeries in the same area in history while in group with spacers such patients constituted only 38,6% ($n = 29$) ($p<0,0001$). At the same time the share of patients with two and more recurrent PJIs in history was 78,9% ($n = 45$) and 25,3% ($n = 19$), respectively, in the study groups ($p<0,0001$).

There were no significant variances between the groups at the moment of hospitalization in terms of systemic inflammation, total protein level and hemoglobin (table 1). Anemia rate in AMS group was 57,3% and in PMF group — 64,3% ($p>0,05$), rate of hypoalbuminemia was 31,1 and 57,1% ($p>0,05$), hypoproteinemia — 25,7 and 30,9% ($p>0,05$), respectively. Time of surgery in group PMF was longer ($p<0,05$) than in AMS group due to an additional stage of isolation and transfer of a pedicle muscle flap. At the same time volume of intraoperative blood loss were comparable; drainage blood loss was higher in patients with grafting of axial muscle flap ($p<0,05$). In both group the majority of defects in the hip joint were considered small but it should be noted that group PMF featured 65% of such defects in contrast with 80% in AMS group ($p = 0,051$). Large and irregular defects were observed more often in group PMF however without statistically significant differences from AMS group.

No significant differences were observed in the structure of microbial agents of DTT PJI between the groups. The infection in the vast majority of patients in the both groups was due to microbial association (table 2): 77,2 and 72,0% in PMF and AMS groups, respectively. Gram-negative bacteria were isolated in microbial association in 32 out of 44 cases (72,7%) for PMF group, and in 48 out of 54 cases (88,9%) for AMS group, MRS (methicillin-resistant staphylococci (MRSA+MRSE)) in 16 out of 44 (36,4%) and in 20 out of 54 (37%) cases, respectively. Share of patients with polymicrobial infection caused by two and more DTE agents was higher in PMF group (21,1%) in contrast to AMS group (9,3%), however, these variances were of no statistical significance ($p = 0,08$).

S. aureus and *S. epidermidis* held the biggest share in type composition of pathogens, namely 37,2 and 31,6% in PMF and AMS groups, respectively, (table 3). Isolation rate of methicillin-resistant strains in the groups did not vary significantly and constituted 40,4% and 42,9% for MRSA, and 54,5% and 73,1% for MRSE in PMF and AMS groups, respectively. High isolation rate of nonfermentable bacteria (22% and 20,4% in PMF and AMS groups, respectively) as well as members of Enterobacteriaceae family (21,2% and 22,8%, respectively). *K. pneumoniae* strains constituted slightly less than a half in the enterobacteria spectrum: 42,9% and 35,9% in PMF and AMS groups, respectively.

Table 1

Characteristics of clinical comparison groups

Parameters	PMF group	AMS group	p
Total, *n*	57	75	–
Male, *n*	33 (58%)	36 (48%)	0,26
Female, *n* (%)	24 (42%)	39 (52%)	>0,05
Age, years, Me (25–75% IQR)	59 (52–67)	62 (52,5–69,5)	0,3
Medical History			
Duration of PJI, days, Me (25–75% IQR)	629 (265–1276)	350 (82,5–1229)	0,03
2 and more recurrences in history, *n* (%)	45 (78,9%)	19 (25,3%)	<0,0001
3 and more recurrences in history, *n* (%)	51 (89,4%)	29 (38,6%)	<0,0001
Laboratory data prior to surgical procedure			
Total protein, g/l, Me (25–75% IQR)	68,0 (64,0–76,0)	69,0 (65,0–74,0)	0,9
Hemoglobin, g/l, Me (25–75% IQR)	110,0 (101,0–125,0)	116,0 (105,0–129,0)	0,07
WBC level, $\times 10^9$ /l, Me (25–75% IQR)	6,4 (5,7–7,7)	7,3 (6,0–8,6)	0,05
ESR, mm/h, Me (25–75% IQR)	55,0 (35,0–82,0)	48,0 (29,0–68,0)	0,14
CRP, mg/ml, Me (25–75% IQR)	33,0 (24,0–58,0)	29,0 (14,0–52,0)	0,35
Fibrinogen, g/l, Me (25–75%IQR)	4,3 (3,8–5,2)	4,1 (3,6–4,9)	0,17
Intraoperative data			
Time of procedure, min	220 (180–250)	195 (160–228)	0,03
Total intraoperative blood loss volume, ml	700 (500–1000)	800 (500–1300)	0,2
Drainage blood loss volume, ml	600 (450–860)	500 (400–600)	0,003
Small defects of hip joint, *n* (%)	37 (65%)	60 (80%)	0,051
Large defects of hip joint, *n* (%)	4 (7%)	1 (1,3%)	0,17
Irregular defects of hip joint, *n* (%)	16 (28%)	14 (18,7%)	0,22
Outcomes			
Secondary debridement of postoperative wound during first 30 days, *n* (%)	20 (35%)	21 (28%)	0,384
PJI remission, *n* (%)	55 (96,5%)	34 (45,3%)	<0,0001
Late recurrences, *n* (%)	2 (3,5%)	20 (26,7%)	0,004

Me — median; IQR — interquartile range.

Table 2

Etiology features of difficult-to-treat PJI in the groups

Characteristics of infection agents	PMF group	AMS group	*p*
Monobacterial infection			
Total, *n* (%)	13 (22,8%)	21 (28%)	0,55
With gram (+)	7 (12,9%)	10 (13,3%)	1,0
With gram (-)	6 (10,5%)	11 (14,7%)	
Microbial associations			
Total, *n* (%)	44 (77,2%)	54 (72%)	0,55
With MRS	16 (28,1%)	20 (26,7%)	0,65
With gram (-)	32 (56,1%)	48 (64,0%)	
Two and more infection agents difficult to eradicate	12 (21,1%)	7 (9,3%)	0,08
Total	57	75	–

Table 3

Type composition of main infection agents in the groups

Type of infection agent	PMF group		AMS group		*p*
	Абс.	%	Абс.	%	
Staphylococcus aureus	27	20,5	28	16,4	0,361
Staphylococcus epidermidis	22	16,7	26	15,2	0,73
Acinetobacter sp.	19	14,4	24	14,0	1,0
Pseudomonas aeruginosa	10	7,5	11	6,4	0,82
Fam. Enterobacteriaceae	28	21,2	39	22,8	0,78
Fungal infection, including, *Candida*	3	2,3	2	1,2	0,66
Other	23	17,4	41	24,0	1,0
Total, strains	132	–	171	–	–

During analysis of late outcomes after resection hip arthroplasty in combination with grafting by vastus lateralis pedicle muscle flap it was observed that at mid-term follow up of 6,2 years (IQR 4,507,3) the efficiency of eradication for DTT PJI was 96,5% (*n* = 55). It should be noted that in 7 cases (12,3%) in follow up period from 2,1 to 5,1 years after grafting the patients successfully underwent revision hip arthroplasty without signs of recurrent infection during a period from one to 4,2 years. Infection remission in AMS group was achieved in 45,3% of cases (*n* = 34) followed to second stage of surgical procedure: spacer removal and implantation of prosthesis. Median of the interval between the stages was 237 days (IQR 139-364). Patients with recurrent PJI after implantation of an antimicrobial spacer in 68,3% of cases (28 out of 41) underwent secondary sanation procedure with re-implantation of antimicrobial spacer, in 17,1% of cases (7 out of 41) — resection arthroplasty, in 14,6% of cases (*n* = 6) — resection arthroplasty with grafting by vastus lateralis pedicle island muscle flap.

It's worth noting that 35% of cases in PMF group (n = 20) required secondary revision of postoperative wound in early postop period (Me = 10 days, IQR 7,5-15). Main reasons for revision were formation of culture negative hematoma (n = 6), recurrent PJI (n = 9), partial of complete necrosis of the muscle flap (n = 5). However, after secondary revisions all patients were discharged with wounds healed by primary tension. Early recurrent PJI in group AMS was observed in 28% of cases (n = 21) that required secondary sanation.

Evaluation of late treatment outcomes in PMF group revealed only 2 cases (3,5%) of recurrent infection manifested by fistula at the surgical site with occasional purulent discharge. Delayed recurrent infection in AMS group was diagnosed in 26,7% of cases (n = 20) at the admission for the second stage of surgical treatment in average of 165 days (IQR 82-344) after sanation procedure.

Discussion

Today the two-stage procedure of revision with a long interval (>6 weeks) between the stages is considered the most rational treatment option for difficult-to-treat PJI [1, 15]. A longer period of exposure of infection focus to the antibiotic added to the bone cement is considered as one of the possible grounds for increased interval between the surgical stages. At the same time, it was demonstrated that antibiotic loaded cement spacers can act as foreign bodies enabling microbial biofilms to grow on them despite a high local concentration of the antibiotics within first several days after implantation [16].

The majority of publications confirm reduced treatment efficiency for PJI caused by polyresistant bacterial strains and/or microbial associations irrespective of surgical methods applied [5, 6, 8]. D. Akgün et al take a different view. When analyzing PJI treatment efficiency in 163 cases where 30 cases were caused by pathogens resistant to antibiotics with antibiofilm effect the authors did not observe any influence of indicated pathogens on the infection eradication rate. With two year follow up absence of infection was reported for 80% of patients (95% CI 61–90%) in the group of DTT PJI and for 84% of patients (95% CI 76–89%) in comparison group (p = 0,61). It should be taken into account that in the abovementioned study the group of DDT PJI included patients with infection induced by enterococci (n = 18), rifampicin-resistant *Staphylococcus epidermidis* (n = 10) and fungi (n = 3). One case of association of *Enterococcus faecalis* and *Candida albicans* was reported. There were no patients with DTT PJI induced by gram-negative bacteria in the mentioned study [15].

In the present study gram-negative bacteria constituted 43,2% in the type composition of both study groups; microbial associations were identified in more than 70% of cases, while according to the data of the same authors from earlier studies and according to data of the other researchers the presence rate of gram-negative bacteria as well as microbial associations in the patient cohort with hip PJI constitute 15-20% [17]. This fact can be explained by the growing fluoroquinolone resistance of *K. pneumoniae*, *Acinetobacter sp.* and *P. aeruginosa* which in the period of 2016-2017 amounted to 93,1%, 87,7% and 56,1%, respectively, and was associated in majority of strains with resistance to other classes of antibiotics [17].

T. Rosteius et al [3] also noted the tendency to a growing number of highly resistant PJI-inducing agents such as MRSE, extended-spectrum beta-lactamase producing bacteria, ampicillin-resistant enterococci, *Acinetobacter spp*. and vancomycin-resistant enterococci. Apparently, the resistance level significantly affects the treatment outcome irrespective of surgical tactics. Thus, research group of A.Papadopoulos et al analyzed the treatment efficiency of 131 patients with PJI caused by polyresistant (n = 108) and extremely resistant (n = 23) strains of gram-negative bacteria and dem-

onstrated a significantly reduced rate of infection eradication in PJI group with extremely resistant pathogens (p = 0,018): from 79,6 to 60% after sanation and removal of prosthesis, and from 53,7 to 23,1% after sanation and preservation of the prosthesis. Obtained results also prove that sanation and preservation of implants in such type of PJI features very low efficiency and should not be considered as the treatment of choice [2].

Thus, the authors of the present paper suggest that PJI treatment outcomes are influenced not by the resistance to antibiotics with antibiofilm action but the overall resistance level of the pathogen: the smaller is the class of antibiotics active against particular strain of PJI-inducer the worse is the treatment outcome. This is confirmed by current lack of efficient therapy algorithms for treatment of infectious complications caused by extremely resistant gram-negative bacteria [18, 19, 20].

In the present study with twice higher share of high resistant gram-negative pathogens (as compared to average population of PJI patients) the efficiency of infection eradication after sanation with spacer implantation was rather low of 45,3% at the moment of patients' admission for the re-insertion of prosthesis during second stage of treatment. At the same time, despite high number of microbial associations with two and more pathogens resistant to antibiotics with antibiofilm effect, in MPF group the authors managed to stop infection in 73 out of 75 cases (96,5%) and gain stable remission with mean follow up of 6 years, and in 7 cases — to successfully perform reimplantation of prosthesis.

So, the risk of delayed recurrent infection after sanation procedure followed by insertion of antimicrobial cement spacer in patients with DTT PJI caused by DTE bacteria exceeds more than 7,5 times the risk of recurrent infection after resection arthroplasty combined with vastus lateralis pedicle island flap (RR 7,6; 95% CI 1,851–31,197; p<0,05). At the same time, chances to obtain remission of DTT PJI in one year and more after sanation and antimicrobial spacer are ten times less than after grafting by pedicle muscle flap (OR 0,1; 95% CI 0,022–0,449; p<0,05). The obtained data supports the assumption of W. Zimmerli et al that two-stage surgical treatment with interval without a spacer is more favorable in cases of difficult-to-treat infection [21].

It should also be noted that early postoperative period in both groups was complicated. In particular, secondary procedure due to recurrent PJI in early postoperative period (infected hematoma, wound dehiscence, intensification of infection signs) was required in 15,8% and 28% of cases after muscle grafting and AMS insertion, respectively (RR 2,66; 95% CI 1,149–6,158; p<0,05). Probably, the higher rate of infected hematomas formation was related to residual cavity of 20–50 cm^3 in the joint after removal of implants and insertion of a spacer as well as due to insufficient antibiotics concentration in the infection focus. At the same time transferred island muscle flap adequately replaced the cavity in the surgical wound in the majority of cases and provided sufficient perfusion for surrounding tissues. However, we should mention partial or complete necrosis of muscular flap as one of possible complications after grafting which in the present study was reported in 5 (8,8%) cases.

It is known that in certain cases of chronic osteomyelitis of various locations the muscle grafting is used to replace bone cavities [22, 23, 24, 25]. This is largely due to the fact that grafting by pedicle island muscle flap guarantees high perfusion of transferred muscle tissue facilitating good delivery of white blood cells, oxygen and antibiotics to the infection focus [13]. One the one hand, this contributes to eradication of PJI inducing agents, but, on the other hand, along with large area of surgical wound is the reason for a larger volume of drainage blood loss in early postoperative period in PMF group in contrast to AMS

group (p = 0,003). In 6 out of 57 cases (10,5%) this resulted in formation of culture negative hematoma and need for revision of postoperative wound.

So, the discussed surgical method for treatment of patients with DTT hip PJI requires further research despite good results obtained from the conducted comparative analysis. In particular, the authors consider necessary to optimize mode of anticoagulants administration aimed at reducing the volume of intraoperative blood loss and risk of large hematomas by maintaining at the same time the efficient prevention of thromboembolic complications in postoperative period.

The conducted comparative analysis demonstrated that sanation surgery with implantation of an antimictobial spacer in patients with PJI caused by DTE pathogens resulted to recurrent infection in more than half of the cases. At the same time stable infection remission was achieved in 96,5% of cases despite a lengthier and complicated treatment of DTT PJI in patients who underwent resection hip arthroplasty in combination with pedicle island muscle flap. Obtained results allow to consider the present operative procedure as a surgery of choice for cases of recurrent DTT PJI with possible re-implantation of prosthesis along with stable infection remission. However, we should consider possible and rather frequent complications: formation of culture negative hematomas, recurrent infection, partial or complete necrosis of the muscle flap, all of which require further improvement of the treatment algorithm for such patients.

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Authors' contribution

V.N. Liventsov — collection and processing of material, statistical processing.

S.A. Bozhkova — concept and study design, editing.

A.Yu. Kochish — concept and study design, editing.

V.A. Artykh — collection and processing of material.

V.L. Razorenov — collection and processing of material.

D.V. Labutin — statistical processing.

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