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Management of aseptic nonunions and severe bone defects: let us get this thing healed!

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Summary: Effective nonunion and bone defect management requires consideration of multiple potential contributing factors including biomechanics, biology, metabolic, and patient factors. This article reviews these factors as well as several potential nonunion or bone defect treatments including bone grafts, bone graft substitutes, the induced membrane technique, and distraction osteogenesis. A summary of these concepts and guidelines for an overall approach to management are also provided.

Keywords: nonunion, biomechanics, fracture healing

1. The Biomechanics of Nonunion Etiology and Treatment

The biomechanical environment is a critical component in fracture healing. A poor biomechanical environment increases the likelihood of fracture nonunion. Fracture nonunion occurs for multiple reasons, all of which should be addressed, but the biomechanical environment that the surgeon creates during the nonunion surgery is the perhaps most critical aspect that they have control over. Returning to standard fracture management principles, correcting any pre-existing deformity, and sometimes changing the fracture-specific environment through osteotomy can be required to successfully treat fracture nonunions.

To successfully discuss how nonunions occur and are treated, we need to ensure that everyone starts on the same page regarding terminology. In this article, a nonunion is considered present when the Food and Drug Administration (FDA) definition is met: a fracture that persists for a minimum of 9 months AND has not demonstrated progression of healing for the last 3 months.[1] Stability is a surgical concept that currently is not measurable. It is the relationship between an applied load and the effect on the mechanical construct.[2] This article will also discuss basic biomechanical terms that surgeons need to be familiar with such as stress–strain, Young modulus, fatigue, working length, bending stiffness, and construct strength.[2]

When nonunions are being managed, an appropriate biomechanical environment is required for healing. Classically, bone healing was believed to require 3 components including osteogenic cells, growth factors, and a scaffold (often referred to as the Triangular Concept)[3]; however, Giannoudis et al[3] proposed the "diamond" concept to include the biomechanical environment which is particularly relevant in hypertrophic nonunions. Although the other parts of the diamond are important, the biomechanical environment can be critical to successful fracture nonunion healing (see Fig. 1).

1.1. Using Biomechanics to Heal Nonunions

Although there are specific laboratory and imaging evaluations for nonunion,[4] we will focus on the biomechanics of nonunion management. Infection should be managed, blood flow maximized, and the soft tissue envelope and biomechanical environment optimized. From a biomechanical standpoint, nonunions may occur when standard fracture management principles are disregarded.[2] For example, if a simple fracture is not reduced and compressed and a gap is left with rigid fixation, healing is less likely to occur because of the high strain environment. Similarly, if there is pre-existing deformity or post-treatment malalignment, nonunion may occur due to a poor biomechanical alignment that creates shear stress on the fracture site. Finally, either the fracture location or pattern can increase the likelihood of a biomechanically disadvantaged situation, such as a high angle transcervical femoral neck fracture in a 23-year-old man (see Fig. 1), and nonunion is more likely to occur in such a setting. Therefore, to minimize the risk of nonunion, standard fracture management principles need to be adhered to achieve an appropriate reduction and limb alignment. Sometimes pre-existing deformity needs to be addressed to improve the fracture environment, and on occasion, it is appropriate to create deformity to improve the biomechanical fracture healing environment (such as performing a valgus-producing intertrochanteric osteotomy to address a transcervical femoral neck fracture nonunion, see Fig. 1).

1.2. Conclusion

Multiple factors affect fracture healing, but recognizing the role of biomechanics in the etiology of fracture nonunion can help the

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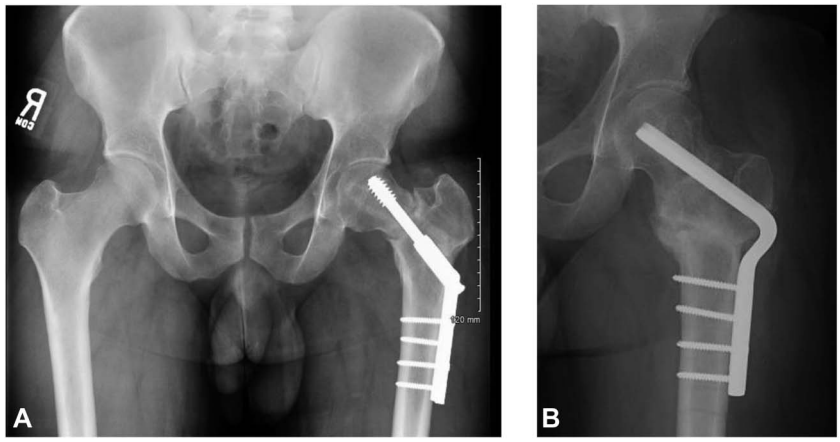

Figure 1. A, Preoperative radiograph of a 23-year-old man with a nonunion of a high Pauwel angle femoral neck fracture. B, Union was achieved 1 year after a valgus-producing intertrochanteric osteotomy.

surgeon identify what needs to be done to create a more positive biomechanical environment that leads to fracture union.

2. Management of Bone Defects With the Induced Membrane Technique

The induced membrane technique for bone defect management allows for osseous regeneration within a potential space surrounded by granulation tissue that arises in reaction to a foreign body spacer.[5] This membrane contains and protects graft material from resorption and allows for sterilization of the wound by way of local antibiotics delivered through the spacer. Induced membranes can be used anywhere in the body to regenerate skeletal tissue, although long-bone diaphyseal and metadiaphyseal defects are the most common indication. It is in these long-bone segmental defects where the convenience of this alternative to prolonged external fixation for bone transport–mediated distraction osteogenesis (DO) is most appreciated by patients and the care team.

There are specific principles that guide the successful implementation of this technique. The wound bed should be cleaned of devitalized tissues, contamination, and infection. Skeletal stability should be maintained throughout the membrane induction and graft consolidation phases. Finally, vital soft tissue coverage and dead space management should be meticulously tended to either through primary wound closure or use of soft tissue flaps (see Fig. 2).

The first stage of this technique requires thorough debridement of foreign body contaminants and devitalized tissue in the case of acute injury or infected and/or necrotic tissues in the setting of nonunion. If the zone of injury continues to evolve or there is suspicion for residual contamination of the wound bed, then sequential debridement procedures should be undertaken until

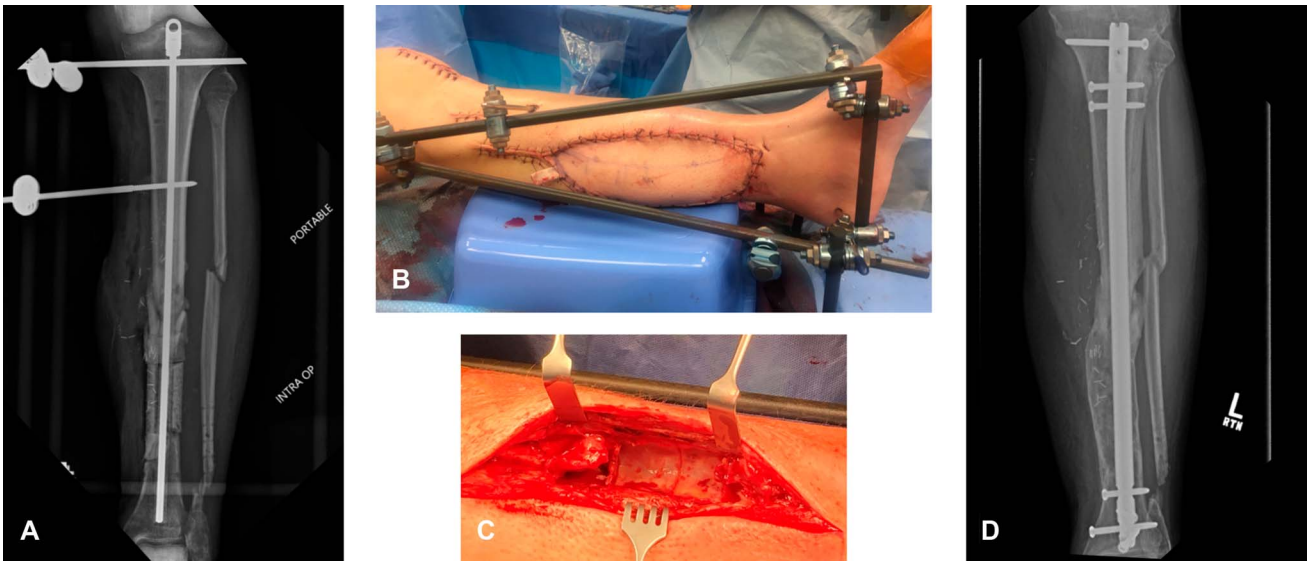

Figure 2. A, B, Radiograph and clinical photograph after first stage of induced membrane technique in a 62-year-old man. The patient was referred 8 weeks after a grade 3 open tibial fracture with a draining sinus and devitalized bone and soft tissue. After initial debridement, first-stage treatment consisted of external fixation, antibiotic nail placement, use of an antibiotic cement spacer for the 10-cm bone defect, and soft tissue coverage with a free anterolateral thigh flap. C, Clinical photograph of the induced membrane at second-stage surgery 7 weeks later. The defect was subsequently grafted with RIA graft combined with allograft. D, Follow-up radiograph at 3 years demonstrating solid radiographic union. The patient was fully weight-bearing, without any pain or recurrence of infection.

there is confidence that all nonviable or infected bone and soft tissues have been removed. The size of the soft tissue and bone defects should be assessed and used to plan for spacer sizing and configuration, dead space management, and coordination with plastic surgeons should additional soft tissue reconstructive procedures be indicated.

Next, provisional [or definitive] stabilization should be achieved to promote soft tissue healing and formation of the induced membrane. Both internal and external fixation can be used; however, avoiding deep foreign body burden when there is high risk for infection is prudent at least during the membrane induction phase of treatment with external fixation and antibiotic-coated medullary devices. In the case example shown, infection involving the medullary canal and the distal tibia and the adjunctive stabilization of a medullary implant indicated use of hemicylindrical spacers around a 6-mm threaded rod coated with antibiotic impregnated methyl methacrylate cement (see Fig. 2). While Masquelet does not advocate for the use of antibiotics in bone cement, and the clinical importance of varying antibiotic choices and concentration on membrane bioactivity has not been fully understood,[6] consideration should be given to using spacers for local antibiotic delivery whenever the potential for fracture-related infection exists.

The final step in membrane induction is dead space management and viable soft tissue closure. This can be achieved primarily or by way of soft tissue reconstructive techniques including skin grafting or local and free tissue transfer (see Fig. 2). Both animal and human studies have shown high expression of growth factors and angiogenesis at 4–6 weeks from spacer placement and soft tissue closure[7,8]; therefore, spacer removal and grafting of the defect should be undertaken within 1 to 1.5 months. The membrane should be incised longitudinally and handled carefully so as to allow for closure and containment of graft material. Autogenous bone graft remains the gold standard based on the best available evidence from randomized controlled trials in human subjects.[9,10] For large volume defects, medullary bone from the femur can be harvested and extended with allograft as an extender for large volume defects.[11] It is the authors' preference to protect weight-bearing until cortical bridging is detected followed by partial progressive loading. Close clinical follow-up is required until union which may require more than 1 year depending on the length, location, and geometry of the bone defect.

The induced membrane technique is nuanced and is necessarily variable based on the bone location, circumference of the defect, soft tissue condition, and host factors. Still, the principles listed above apply broadly. Regardless of the spacer material or graft choice, the induced membrane is osteoinductive in providing vascularity and secretion of growth factors that support graft incorporation and mesenchymal stem cell differentiation. It is also osteoconductive in serving as a substrate for both intramembranous ossification and cartilage formation. The power of this technique to successfully treat defects averaging 6 or more centimeters with success rates of 70%–90% have led some to argue against an "upper limit" to the length of defects that can be successfully treated.[11,12] Because graft incorporation and remodeling must necessarily progress inward from the membrane to the core of the graft [or medullary implant], maximizing the surface area relative to the volume of graft material improves the odds of successful healing using the induced membrane technique. More rigorous basic and clinical investigations are required to elucidate the optimal spacer material, graft choice, and operative indications for this technically demanding procedure for bone reconstruction.

3. Biologic Treatments for Nonunion: Bone Graft Types and Distraction Osteogenesis

There is little evidence and a distinct lack of consensus regarding both the definition and management of critical-size bone defects for acute traumatic and reconstructive nonunion deficiencies.[13] Most studies are difficult to stratify because they include both infected and noninfected defects and may or may not comprise nonunion with associated soft tissue defects. With the widespread use of orthobiologics in everyday practice, attention must be directed to substantiate the evidence for their current use when treating nonunions with or without bone defects.

3.1. Autogenous Bone Graft

Fresh cancellous autograft provides the quickest and most reliable type of bone graft. Its open structure allows rapid revascularization; a 5 mm graft may be totally revascularized in 20–25 days. These grafts depend on ingrowth of host vessels and perform best in well-vascularized beds. The large surface area of harvested autograft allows for survival of numerous graft cells. It is estimated that approximately 30 mL of graft can reliably be harvested from an anterior iliac crest (AICBG).[14] Studies document success rates approaching 100% for subcritical sized defects and nonunions (1 to 2 cm defects) requiring 20 mL or less of autograft.[15] Tibial defects in the order of 2.5 cm or greater have a poor natural history when AICBG is being used, and the rates of union drop significantly for larger defects with success being potentially limited by harvest volumes. The reamer irrigator aspirator (RIA, Depuy Synthes; Paoli, PA) offers a technique to achieve substantial amounts of graft volumes for the treatment of larger segmental defects. Medullary autograft cells harvested using RIA are viable and osteogenic. Cell viability and osteogenic potential are similar between bone grafts obtained from both the RIA system and the iliac crest, and both are excellent sources for autogenous bone graft, the gold standard for augmentation of fracture healing.[16]

3.2. Demineralized Bone Matrix

Demineralized bone matrix (DBM) is used widely as an osteoconductive substrate and is often used as an adjuvant to the fracture site when treating acute fractures. It contains type-1 collagen, non-collagenous proteins, and osteoinductive growth factors including the bone morphogenic proteins (BMPs) and other inductive factors found in the transforming growth factor-beta (TGF-β) group of proteins. DBM is highly osteoconductive due to its particulate nature and presents a large surface area and three-dimensional architecture to serve as a site of cellular attachment.[17,18] These characteristics give DBM advantages for use as a cellular matrix delivery material. DBM is, strictly speaking, allogeneic bone tissue. Most clinical series combined DBM with other adjuvants, and the singular effectiveness of DBM alone is difficult to elucidate.

3.3. Bone Marrow Aspirate Concentrate

Bone marrow aspirate has been used as a source of bone marrow–derived mesenchymal stem cells (MSCs) with its relative ease of harvest and low morbidity. The aspirate is typically concentrated by centrifugation to increase the ratio of MSCs. Bone marrow aspirate concentrate (BMAC) provides both stem cells and growth factors. Current use relies on the development of a "composite graft," which involves loading the BMAC onto a highly osteoconductive carrier with a specific three-dimensional architecture to facilitate cellular attachment for graft delivery.[19] Common materials include cancellous allograft, DBM, and particulate calcium phosphate

Table 1.

Multifactorial Approach to Nonunion Management (modified from Hoit et al)[26]

Potential Factor in Development of Nonunion	Examples	Diagnostic Tests	Treatment Required
Biomechanical	Loose/failing hardware, malreduction/ malalignment, inappropriate construct choice	Radiographs	Hardware revision, biomechanical augmentation
Biological	Impaired vascularity, extensive soft tissue damage, long-term bisphosphonate use, other causes of poor healing capacity	Radiographs (atrophic nonunion, initial severity of injury)	Biological adjuvants (autogenous bone graft, BMP, PDGF)
Metabolic	Vitamin D deficiency, calcium imbalances, central hypogonadism, thyroid disorders, and PTH disorders	Metabolic and endocrine-related laboratory tests[27,28]	Referral to rheumatology or endocrine to correct any abnormalities identified
Patient factors	Smoking, malnutrition, diabetes	History, albumin levels, HbA1c	Smoking cessation, nutritional supplementation, glucose control
Infection	Chronically infected hardware and/or bone	Radiographs, esr, crp, wbc, deep tissue cultures	Removal of all hardware, irrigation and debridement, local and systemic antibiotic treatment

BMP = bone morphogenetic protein; HbA1c = hemoglobin A1c; PDGF = platelet-derived growth factor; PTH = parathyroid hormone.

ceramics as porous carrier materials. Current literature demonstrates perhaps faster healing times with similar union rates when using BMAC combined with allograft compared with conventional autologous cancellous bone graft.[19] There continues to be discrepancies in the literature regarding the method of centrifugation, variable cell count concentrations, and lack of standardized outcome measures. Although several studies have evaluated the effect of cell concentration on healing potential, an effective therapeutic range has yet to be established for nonunion treatment.

3.4. Bone Morphogenic Protein

Developments in bone tissue engineering and bone biology have revealed the unique advantages of BMPs for bone tissue repair. BMPs promote bone healing by inducing mesenchymal stem cells to differentiate into osteoblasts. Currently, only BMP-2 (INFUSE™ Bone Graft, Medtronic, Minneapolis, MN) is available for clinical application. FDA-approved indications for INFUSE™ bone graft include use in open tibial shaft fractures and spinal fusion. Despite the initial enthusiasm for the use of BMPs for nonunion treatment, the evidence has not demonstrated the clinical superiority of these materials over autograft. BMP does not significantly improve the final extent of healing or change the rates of union compared with AICBG. The addition of BMP to AICBG has been shown to decrease healing times, although treatment cost is much higher and the addition of BMP does not influence the infection rate or rate of secondary surgery. BMP may reduce donor site complications and may provide an alternative option for patients with poor donor bone quality or poor surgical tolerance for graft harvesting. However, the current evidence does not support the widespread use and application of BMP for improved outcomes in nonunion surgery.

3.5. Platelet Concentrate and Platelet Derived Growth Factor (PDGF)

Currently, there is no Level I evidence to indicate using PRP alone or in combination with other materials has a substantial effect on bone healing. Overall, there is clearly a lack of scientific evidence to support

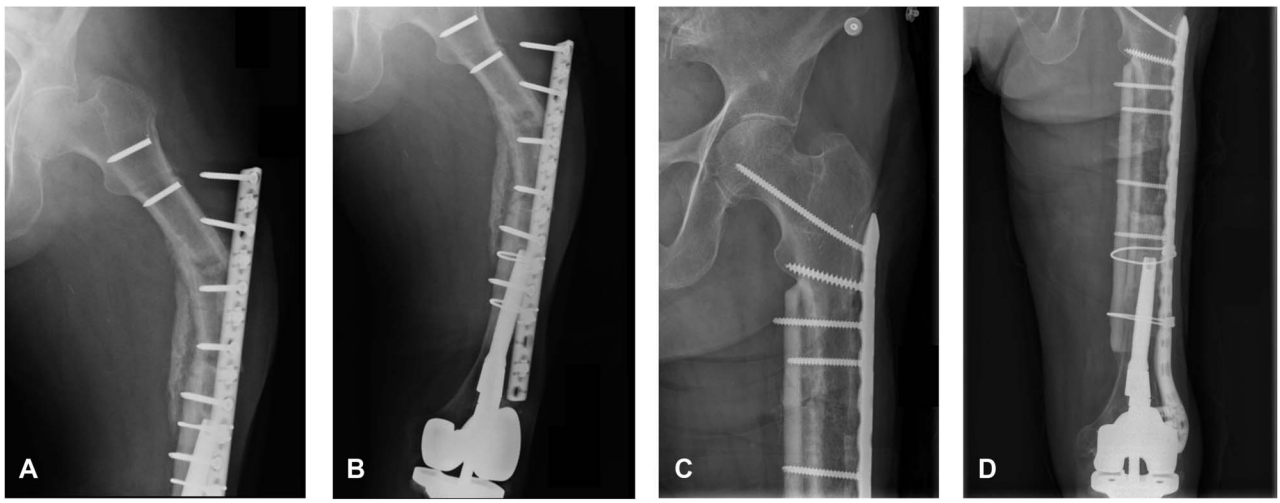

Figure 3. A, B, Preoperative radiographs of a femoral nonunion in a 76-year-old female patient with a history of stemmed total knee arthroplasty. The patient had undergone 2 previous attempts at fixation of her femoral fracture, both of which had failed. She was subsequently referred for treatment. Preoperative workup identified low vitamin D and malnutrition. Treatment of this was instituted before repeat surgical intervention, during the same hospital admission. Her radiographs demonstrated failed fixation and varus collapse. C, D, Revision fixation was performed with a longer plate spanning the entire femur and the addition of a femoral allograft strut placed medially to improve the biomechanics of the construct. In addition, bone morphogenic protein (BMP-2, INFUSE™ Bone Graft, Medtronic, Minneapolis, MN) was placed at the nonunion site to provide additional biology. Radiographs at 1-year postrevision surgery demonstrate healing of the nonunion with graft incorporation and maintained anatomic alignment.

the use of PRP in combination with bone grafts during nonunion procedures.[20] The one area that platelet concetrate/PDGF has demonstrated promising results is for the augmentation of fractures and fusions in diabetic foot and ankle patients. Multiple RCT's (Level I) studies have demonstrated efficacy in patients requiring hindfoot or ankle arthrodesis and repair of recalcitrant foot and ankle nonunions. Treatment with rhPDGFBB/beta tri-calcium phosphate (β-TCP) (AUGMENT® Bone Graft, Wright Medical, Franklin, TN) resulted in comparable fusion rates and less pain, when compared with treatment with autograft.[21]

3.6. Calcium Ceramics

There is considerable interest in creating osteoconductive matrices using nonbiological porous structures implanted into or adjacent to bone. The host substrate must mimic the cancellous bony architecture and have very specific surface kinetics to facilitate the migration, attachment, and proliferation of mesenchymal stem cells, which then differentiate into osteoprogenitor cells.

Broad categories of these materials are available and in general are classified as calcium ceramics. These include the specific materials of calcium sulfate and phosphate, synthetic tricalcium phosphate as well as beta tricalcium phosphate, and coralline hydroxyapatite.

These materials have been used successfully for the augmentation of subchondral defects when used with internal fixation for repair of articular injuries. Because of their porous structure, they are the ideal matrices for the delivery of cellular concentrates and many of these materials have been used as the carrier component for composite bone graft materials in combination with BMAC.[22]

3.7. Distraction Osteogenesis

Bone transport with distraction osteogenesis (DO) has proven to be a powerful tool for reconstruction and can eradicate infection, compensate bone defects, and promote bone union through progressive tissues histogenesis. These techniques have been used and consistent results obtained for nonunion defects up to 10 cm. Traditional methods of DO using ring fixation with wires or half pin methodologies are being supplanted by recent advancements in transport methodologies. This includes using hexapod frames with computer-assisted programs, internal cable transport of bone segments, and transport over plates and nails. The advent of a totally implantable bone transport nail now allows management of critical bone loss defects by DO negating the need for external fixation and avoiding its negative effects.[23]

4. Putting It all Together: Principles of Nonunion Management

Successful nonunion management requires a comprehensive assessment of potential contributing factors to the development of nonunion. The occurrence of nonunion is often multifactorial as multiple investigators have previously pointed out.[4,24,25] Achieving union commonly requires that multiple factors are identified and addressed with any treatment and revision surgery. The authors assess patients presenting with nonunion using a standardized algorithm to identify potential contributing factors and subsequently develop a customized approach to each patient that treats all the potential contributors with a comprehensive treatment strategy. Table 1 outlines such an approach, including examples, diagnostic tests, and potential treatments.[26]

Whenever possible, any patient or metabolic factors that can be optimized to improve the healing response should be addressed before undertaking surgical intervention. This may include interventions listed in Table 1 such as vitamin D supplementation, endocrinology referral, smoking cessation, nutritional optimization, and/or diabetic control. In a patient with stable hardware, there is typically sufficient time to identify and correct these issues before embarking on surgical treatment. Even most patients with failed hardware present with a fibrous union with sufficient stability to delay surgical treatment until these other factors have been addressed. In those patients with failed hardware who are unable to mobilize sufficiently, the identification and treatment of metabolic and patient factors can be undertaken simultaneously with surgical treatment. There is good quality evidence that the identification and treatment of metabolic factors can significantly increase the success of nonunion treatment.[27,28] When revision surgery is planned, once again multiple factors are taken into consideration to develop an effective surgical treatment plan (see Fig. 3). This includes consideration of biomechanical and biological factors as previously discussed but also consideration of any potential for infection which is a frequent culprit in the etiology of nonunion. In our experience, these complex cases can be managed with a high degree of success when such an approach is followed.

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