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EDITORIAL

# The reconstruction of critical bone loss

## THE HOLY GRAIL OF ORTHOPAEDICS

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**Cite this article:** *Bone Joint Res* 2022;11(6):409–412.

**Keywords:** Bone regeneration, Biologics, Bone loss

The reconstruction of segmental long bone defects demands a substantial investment of time and resources for both patients and healthcare providers.[1] The post hoc analysis of the SPRINT trial has been particularly influential in advancing our understanding of this matter.[2] At present, defects larger than 2 cm in length and with more than 50% circumferential bone loss are considered critical bone defects and unlikely to heal without further intervention.[3] Ferreira and Tanwar[1] recently proposed a classification system and treatment algorithm that considers the size of the bone defect (< 2 cm, 2 to 6 cm, 6 to 12 cm, or > 12 cm), soft-tissue quality (no deficit, defect requiring reconstruction, or unreconstructable defect), and host type (no compromise, local or systemic compromise, or treatment would be worse than the disease for the patient). It is proposed that the subsequent management is tailored to address all the elements identified in the classification system.

Despite progress in our understanding and approach to this clinical problem, there remains equipoise within the orthopaedic community regarding the reconstruction of critical bone defects. In recent years, the induced membrane technique has attracted much attention, both clinically and academically. The approach was first reported by Masquelet et al,[4] who described a two-stage procedure to reconstruct critical-sized long bone defects. Following debridement, a polymethylmethacrylate (PMMA) cement spacer is implanted into the bone defect. During an interval period (typically four to six weeks), the spacer becomes encapsulated by a pseudosynovial membrane. The PMMA cement spacer is removed in the second stage and the defect is filled with non-vascularized autogenous bone graft. The perceived advantages of this technique over primary bone grafting include: 1) preservation of bone length, 2) prevention of soft-tissue interposition within the defect, 3) formation of an encapsulated defect preventing bone graft migration and resorption, and 4) creation of a biological chamber with angiogenic and osteogenic properties at the site of the defect.[5,6] Previous studies have sought to characterize the biological potential of the membrane: Christou et al[7] reported the expression of bone morphogenic protein 2 (BMP2), transforming growth factor-beta, vascular endothelial growth factor, von Willebrand factor, interleukin (IL) 6, and IL 8 within the induced membrane of a critical defect in an ovine model.

In a systematic review and meta-analysis of 48 observational studies that included 1,386 cases treated with the induced membrane technique, Fung et al[8] reported that 82% of cases achieved union after the first grafting procedure, with 87% achieving union after repeated grafting procedures. The mean time to union was 6.6 months (1.4 to 58.7) after bone grafting. There was a requirement for unplanned procedures in 18% and subsequent infection in 10% of cases. In a sub-analysis of 450 individual patients, multivariate analysis identified the presence of preoperative infection as the primary risk factor for nonunion of the defect. Patients with tibial defects, and those with larger defects, were at statistically significant higher risk of developing postoperative infection.[8]

Despite the risk of nonunion in the presence of infection, as reported by Fung et al,[8] the reported outcomes of the induced membrane technique used to manage bone loss in the treatment of post-traumatic osteomyelitis have been favourable. Wang et al[9] reported the outcomes of 32 cases (mean defect volume 42 $cm^3$ (9 to 136)) treated over

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doi: 10.1302/2046-3758.116.BJR-2022-0186

*Bone Joint Res* 2022;11(6):409–412.

15 months in Chongqing, China. At a median follow-up period of 28 months (interquartile range 24 to 32), clinical union was achieved in 29/32 cases and radiological union in 26/32. The mean radiological bone healing time was 4.9 months (3 to 9), with the mean time to clinical union being 7.5 months (4 to 14). In a further study from the same institute, the authors described a modification of the induced membrane technique to manage bone loss in the presence of infection. An antibiotic cement-plate composite device was used to provide internal fixation following debridement for osteomyelitis ("Chongqing technique"). In 548 patients treated for osteomyelitis, 83% were infection-free at six months following a single debridement and stabilization. An impressive 95% were infection-free at six months if those undergoing a secondary debridement and fixation with the antibiotic cement-plate construct were included. Those with osteomyelitis involving the tibia were found to have a significantly higher risk of treatment failure ($p = 0.047$). However, when compared to a historical cohort of tibial osteomyelitis stabilized with external fixation treated at the same institution, those undergoing the "Chongqing technique" were found to have a similar risk of treatment failure (21% vs 23%, $p = 0.354$).[10] In a systematic review and meta-analysis of studies investigating the management of critical-sized bone defects in the treatment of fracture-related infection, eight studies that reported the outcomes of the induced membrane technique were identified.[11] The included studies described the treatment of 177 patients, with a mean age of 42 years (16 to 72), a mean bone defect size of 4.5 cm (1.0 to 26.0), and a mean follow-up period of 26 months (13 to 72). All eight studies used a two-stage reconstruction protocol with an antibiotic-loaded cement spacer, which was removed after a mean time of 68 days. A comparative analysis between surgical strategies could not be performed due to the heterogeneity within the pooled patient sample and the lack of a standardized definition of fracture-related infection across the studies. Nonetheless, the meta-analysis was able to report that the induced membrane technique was associated with primary healing in > 80%, bone union > 90% following secondary procedures, time to union approximately eight months, recurrence of infection approximately 15%, amputation in 5%, and complications occurred at a rate of 0.6/patient.[11]

Alternative strategies to the induced membrane technique in managing critical bone defects include bone transport, vascularized fibula grafts, and amputation. Bone transport, as described by Ilizarov,[12] is an established technique in the management of bone defects. The adaptability of circular external fixation facilitates simultaneous management of concurrent soft-tissue defects and deformities. A systematic review and meta-analysis of observational studies, which reported the outcomes of bone transport with a circular frame in the treatment of infected nonunions of the tibia and femur (590 patients in 24 studies), found 97% union with a mean external fixation time of 10.7 months, and external fixation index of 1.7 months/cm.[13] The mean length of the bone defect was 6.5 cm in patients with infected tibial nonunions and 8.0 cm in patients with infected femoral nonunions.[13] In a review of bone transport for treating critical-sized bone defects in the tibia, Aktuglu et al[14] reported outcomes in 619 patients in 27 studies. Infection was present in 88.8% of reported cases. Union was achieved in a mean 90.2% (77% to 100%). The mean bone defect length was 6.5 cm (1.6 to 20) and the mean external fixation time was 10.8 months (2.5 to 23.2).[14]

With certain intramedullary limb lengthening systems,[15,16] there have been concerns regarding peri-implant osteolysis, however the reported outcomes following intramedullary bone transport remain favourable, particularly in the femur where circular frames are less well tolerated.[17-19]

Vascularized fibular grafts have become less popular due to the risk of graft fracture,[14] and the prolonged period of protected weightbearing while awaiting graft hypertrophy. A further barrier is the requirement for expertise in microvascular surgery to perform the procedure. Donor site morbidity is another concern with many reports of muscle weakness, foot pain, and valgus ankle deformity.[20] One technique to mitigate the risk of graft fracture is to harvest the fibula with its peroneal vascular pedicle barring the proximal and distal 5 to 7 cm. The fibula graft can then create a double-barrel construct to allow for more volumetric reconstruction of bone stock. This technique has been reported to decrease the risk of graft fracture and reduce the time of protected weightbearing.[21] A further advantage of the vascularized fibular graft is the ability to include skin, fascia, and muscle to reconstruct concomitant soft-tissue defects.[1]

Amputation should be considered a treatment option rather than a salvage procedure when treatment has failed, especially in Type C hosts. Modern prosthetics have greatly improved the potential functional abilities of amputees, and amputation may lead to better function than a poorly salvaged limb. The outcomes of early primary amputation are comparable to limb reconstruction in the presence of limb-threatening injuries in the lower limb.[22] A systematic review and meta-analysis of observational studies concluded that functional outcomes among patients were not statistically significantly different between limb reconstruction and early primary amputation at a minimum follow-up period of seven years, highlighting the need to optimize triage decisions to avoid unnecessary limb reconstruction procedures and a lengthy journey to amputation.[22]

Currently, there are a host of pre-clinical therapies undergoing development and awaiting translation into clinical practice. Novel osteogenic therapies include coagulated autologous bone marrow aspirate as a source of endogenous reparative cells and growth factors to promote fracture healing.[23] It has been shown to be comparable to autologous bone graft in the regeneration of bone in large segmental defects in a lapine model.[23] Mesenchymal stromal (stem) cells have long been viewed

as a panacea in orthopaedic regenerative medicine.[24] Recent developments have focused on manipulating stromal cells to drive osteogenesis using combinations of growth factors,[25] parathyroid hormone,[26,27] platelet-derived vesicles,[28] bacterial enterotoxin,[29] microRNA,[30,31] and immunomodulation.[32] Pre-clinical osteoinductive therapies include the use of modified messenger RNA (mRNA), the same technology that underpins the Pfizer-BioNtech COVID-19 vaccine, to induce autogenous production of growth factors such as BMP-2.[33] An optimized mRNA sequence for BMP-2 has been shown to recapitulate endochondral ossification in a murine critical bone defect model.[33] Novel mechanistic pathways in the mechanotransduction of bone have been identified and elucidated:[34] knowledge and understanding of these pathways will help to optimize the application of physical therapies such as nanovibriation,[35] low-intensity pulsed ultrasound,[36] extracorporeal shockwave therapy,[37] and pulsed electromagnetic fields[38] in the bid to regenerate bone. Finally, osteoconductive strategies have been facilitated by the application of additive manufacturing technologies,[39-41] which have also been used to improve delivery systems for osteogenic and osteoinductive therapies.[42]

Tissue regeneration in the management of bone defects remains elusive. While many potential therapeutics have been proposed, few have made the transition into clinical practice. Even relatively 'new' surgical techniques, such as the induced membrane/"Masquelet", have been shown to be limited in the hands of the wider orthopaedic community. The ability to regenerate musculoskeletal tissue in a consistent, cost-effective, and clinically acceptable way for patients remains the holy grail of orthopaedic surgery.

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**Funding statement:**
- The authors received no financial or material support for the research, authorship, and/or publication of this article.


**Ethical review statement:**
- Research Ethics Committee approval was not required for this editorial.