Critical-Size Bone Defects: Is There a Consensus for Diagnosis and Treatment?

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Summary: There is a significant burden of disease associated with bone defects, and their management is challenging. These injuries have a profound clinical and economic impact, and outcomes are limited by high rates of complication and reoperation, as well as poor functional outcomes. There remains a lack of consensus around definitions, reliable models, and best practices for the surgical management of bone defects. The current state of the literature on bone defects is reviewed here, with a focus on defining critical-size bone defect, the use of the induced membrane technique, the role of biologics, and the management of infected bone defects.

Key Words: bone defect, critical size, bone graft substitutes, infection, osteomyelitis, induced membrane, Masquelet

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INTRODUCTION

There continues to be a significant burden of disease associated with the management of bone defects, and despite the profound clinical and economic impact of these injuries, their treatment remains controversial. Moreover, long-term outcomes are limited by high rates of complications and reoperations, as well as poor functional outcomes. Despite the need for decision making to be evidence based, a lack of consensus around definitions, reliable models, and best practices for surgical management of bone defects still exists.

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Defining "Critical" in Bone Defect Size

The etiology of bone defects is varied. High-energy trauma with soft tissue and periosteal stripping (particularly in high-grade open tibia fractures), blast injuries, infection requiring extensive debridement, and tumor resection may all be associated with critical bone loss.[1] There is no single definition of what constitutes a critical-sized defect. In general, a "critically-sized" defect is regarded as one that would not heal spontaneously despite surgical stabilization and requires further surgical intervention, such as autologous bone grafting.[1] In a survey of the Orthopaedic Trauma Association membership to determine various aspects of definitive treatment and materials used for grafting in "critical-sized" segmental bone defects, the precise size or volume of bone that comprises a critical-size bone defect was not defined.[2] General guidelines that have been suggested in the literature include defect length greater than 1–2 cm and greater than 50% loss of the circumference of the bone.[1,3] However, this is impacted upon by the anatomic location of the defect and the state of the soft tissues surrounding it.[1] It is also crucial to realize that a nonunion is not the same as a critical-size defect. In a nonunion, there is impaired cellular and molecular signaling and/or biomechanical instability versus a critical-size defect, in which often there is adequate biology and stability but an inability to replace substantial bone loss that may be complicated by the soft tissue environment and patient characteristics.[1–3]

There are numerous factors which affect the capacity of bone defects to spontaneously heal, and their "critical size" is dependent on the absolute versus relative size, whether there is circumferential loss of bone, anatomical location (diaphyseal/metaphyseal/articular), the soft tissue environment, age of the patient, and the presence of chronic disease or other comorbidities.[1–3] Critical-size defects require reconstruction, and the gold standard has been iliac crest bone graft.[1] There are numerous drawbacks of autogenous bone grafting, making it vitally important to determine which defects will heal without additional treatment. The influence of anatomic location is seen when one considers the outcome of segmental defects of the femur versus the tibia. Segmental defects of the femur often have a favorable soft tissue environment, and spontaneous healing of segmental defects 6–15 cm long has been reported.[4] By contrast, poor outcomes with lack of spontaneous healing have been reported with much smaller defects in the tibia, when the defect size is greater than 1–2 cm and greater than 50% of the cortical circumference.[5,6] Defects smaller than this usually are not critical. In the SPRINT trial,

37 of 1125 patients (3%) had a critical-size defect defined as greater than 1 cm in length and >50% of the cortical diameter, however, 47% achieved union without additional treatment.[3] In a study of open tibial shaft fractures treated with an intramedullary (IM) nail by Haines et al, defect size and infection were the main determinants of outcome, and patients who had a radiographically apparent bone gap of less than 2.5 cm achieved union 54% of the time, whereas union did not occur once the defect size was 2.5 cm or greater.[7]

In summary, there is little evidence and a distinct lack of consensus regarding both the definition and management of critical-size bone defects. They are not well defined in most long bones, are multifactorial, and the natural history of smaller defects may be more favorable than traditionally believed. Many defects in the 1–2.5 cm range are not critical sized and are not created equal because close to half may heal spontaneously. Autogenous bone graft is still the gold standard for management, and it remains unclear when alternative biologic therapies should be considered. Tibial defects in the order of 2.5 cm or greater seem to have a poor natural history; however, there is no clear preferred management strategy and there remains a significant evidence gap.

Induced Membrane Techniques (Masquelet) for Bone Defect Management

Reconstruction of bone defects is a complex problem with multiple treatment options including, but not limited to, massive bone grafting, bone transport, free fibula transfer, and amputation. When massive bone grafting is chosen, the use of the induced membrane (Masquelet) technique for bone defect management should be considered. The induced membrane technique allows the management of dead space, the treatment of infection, stabilization for soft tissue healing, and the formation of a biologically active membrane to help stimulate defect healing.

The induced membrane technique is a 2-stage reconstructive procedure. The prerequisites for the procedure include healthy and adequate soft tissue coverage, correction of systemic disease processes where possible, and optimization of the patient's physiologic status. The initial stage of the procedure includes adequate debridement of the affected bone and soft tissue, surgical skeletal stabilization as indicated, and placement of a polymethyl methacrylate (PMMA) cement spacer (with or without antibiotics) at the site of the bone defect. The PMMA spacer serves several purposes; one to preserve a physical space for ultimate bone grafting, second to deliver antibiotics to a previous infected or contaminated bone and soft tissue, and third to induce the formation of the biologically active membrane (see **Fig. 1**, **Supplemental Digital Content 1**, http://links.lww.com/JOT/A296). The second stage typically occurs between 6 and 8 weeks later, with removal of the cement spacer and bone grafting into the preserved defect.

The PMMA spacer induces the formation of a biologically active pseudomembrane that serves to maintain space for eventual bone graft, provides vascularization to the graft, and helps prevent graft resorption. The induced membrane formed is biologically active at the 2–4 weeks mark. At this time, protein levels including vascular endothelial growth factor, transforming growth factor beta, and bone morphogenetic protein (BMP) reach their peak levels and then wane at 6–8 weeks.[8] Further work is needed on characterizing the biologic potential of the pseudomembrane and the best timing for bone grafting. Combining the bioactivity of the membrane with autogenous mesenchymal stem cell–rich bone graft provides the optimal environment to achieve skeletal union. Reamer–irrigator–aspirator (RIA) bone graft from the femur has been shown to be highly biologically active with a substantial number of mesenchymal/progenitor cells.[9] In addition to this, large volumes of bone graft are easily obtainable, and pain at the donor site seems to be less than traditional iliac crest bone graft.[10] For these reasons, RIA bone graft represents an attractive option as a source of autogenous graft.

However, skeletal union remains a challenge to achieve in these settings. Stafford and Norris showed that the combination of RIA bone graft and the Masquelet technique for segmental bone defect management achieved union rates of 70% at 6 months and 90% at 12 months, respectively, in 25 cases with segmental defects averaging 5 cm in length.[11]

Several practical strategies have been suggested to maximize the chances of success when using the induced membrane technique. To minimize required graft volumes and prevent central graft necrosis, some authors have recommended the use of a mesh scaffold or IM nail to occupy the IM canal.[11] If RIA bone graft is selected to fill the bone defect, the flow characteristics of the graft should be addressed by adding material that imparts more structure to the graft; such as iliac crest bone graft, cancellous allograft, and/or calcium phosphate/sulfate structures. In addition, some have suggested that the application of a cage may be beneficial to help hold the graft in place and compartmentalize the revascularization of the graft. Finally, it is important to identify and address those factors that may contribute to recalcitrant nonunion. Ongoing infection remains a common contributor to treatment failure and persistent nonunion. The addition of antibiotics to the cement spacer can be a substantial advantage in this regard. In addition, assessment and treatment of potential complicating patient factors are important aspects of successful management including the evaluation of impaired vascularity (ankle-brachial index and percutaneous oxygen tension), malnutrition/metabolic deficiency (Vitamin D, albumin, and prealbumin), chronic anti-inflammatory medication use, immunosuppressive medication use, and poorly controlled diabetes (HgbA1c).

Bone defects can be effectively treated with the induced membrane technique. To maximize success, strict adherence to the principles of the technique including the eradication of infection, maximizing the bioactivity of the membrane, selecting the optimal bioactive bone graft, and the optimization of host factors is mandatory.

ROLE OF BIOLOGICS IN BONE DEFECT MANAGEMENT

The ability to augment the treatment of bone defects with biologic materials or strategies represents an attractive alternative to conventional treatment options. Several biologic materials or treatments are currently available

for use including cellular therapies with bone marrow aspirate, platelet-rich plasma (PRP), BMP, and distraction osteogenesis.

Bone Marrow Aspirate Concentrate

Concentrated bone marrow aspirate contains a viable population of osteoprogenitor cells that are capable of participating in osteogenesis.[12] This material has been combined with multiple different adjuvants or composites that serve as osteoconductive carriers to deliver the osteogenic marrow elements. This represents a single-step biological strategy for bone defect management. Marrow progenitor cells are harvested from the iliac crest, concentrated in the operating room, and seeded onto an osteoconductive substrate with a microporous structure that provides the cells with a potentially stable and well-vascularized environment. This osteogenic construct is then implanted into the defect.

Scaffolds used have included particulate demineralized bone matrix (DBM), collagen sponges, and porous hydroxyapatite ceramics.[13] A meta-analysis of 249 current basic science studies evaluating BMAC-treated bone defects demonstrated that 100% of these studies showed a statistically significant improvement in bone healing when compared with controls.[14] Hernigou et al reported on the influence that concentration of the bone marrow aspirate by centrifugation had on bone healing.[12] The authors reported excellent rates of union using iliac crest aspirate concentrates combined with and without DBM for the treatment of bone defects up to 3–4 cm. They also reported that significantly lower rates of union occurred in patients who received grafts with less than 1000 progenitors/cm^3 and less than 30,000 progenitors in total. Series using composite grafts of DBM combined with concentrated marrow aspirate have demonstrated results equal to, if not superior to, autogenous iliac crest grafts for the treatment of acute and chronic bone defects of up to 3 cm.[15,16] A recent series demonstrated successful healing of long bone segmental defects of up to 14 cm when treated with BMAC seeded onto bovine DBM scaffolds.[16] Currently, Level 1 clinical evidence for the use of BMAC is minimal. Studies do demonstrate that higher concentrations of bone marrow cells enhance fracture repair, but the maximal defect size that can be treated clinically is unknown.

Platelet-Rich Plasma

Currently, there is no Level I evidence to indicate that using PRP alone or in combination with other materials has a substantial effect on bone healing. The available evidence (Levels III and IV) indicates that PRP may have a positive effect as an adjunct to local bone graft, and its use has been suggested to increase the rate of bone deposition and improve the quality of bone regeneration and fusion in nonunion situations, particularly in foot and ankle surgery.[17] Overall, there is a clear lack of scientific evidence to support the use of PRP alone or in combination with other bone grafts for bone defect management.

Bone Morphogenetic Proteins

The use of inductive proteins (BMPs) has been approved for open tibial shaft fractures and has demonstrated encouraging results for the reconstruction of segmental defects.[18,19] Jones et al used BMP-2 combined with allograft bone for the treatment of acute segmental tibial defects and compared this with a group treated with autograft alone. In this Level 1 clinical trial, the average defect size was 4 cm (up to 7 cm). There were no significant differences in complication rates or functional outcomes between the 2 groups, with similar union rates noted. This study suggested that rhBMP-2/allograft is safe and as effective as autogenous bone grafting for the treatment of tibial defects.

However, other authors have reported limited effectiveness and a significant increase in reported complications related to BMP usage.[20–22] The poorly regulated nature of BMP use has come under intense scrutiny both from third-party payers and governing bodies. Complications seem to be dose dependent, illustrating the need to continue to study this technology.[20] Further research is required to determine accurate dosing and optimal delivery systems to minimize the side effect profile and expand its safe use. Newer and more specific molecules that are effective at lower doses are currently in development.

Distraction Osteogenesis

There are 2 strategies for use of distraction osteogenesis in the face of bone deficits. The first involves acute or gradual shortening and compression at the defect site after contouring the bone ends for stability, followed by corticotomy and lengthening at a separate metaphyseal location. Shortening acutely can be accomplished safely for defects up to 3–4 cm in the tibia and humerus.[23]

A second strategy involves using bone transport to fill the gap while maintaining limb length. The advantage of this strategy is that the limb can be functional, even weight-bearing, during the process.

Bone transport has a high rate of ultimate success, with many series reporting upward of 90% eventually healing.[24,25] However, the treatment can require prolonged times in the external fixator, in some series up to 2 months per centimeter of bone defect. Substantial time is due to delayed healing of the docking site, which frequently requires bone grafting.

Advances include transport over IM nails or plates and using auto distractors that serve to shorten the fixation time. Bone transport IM nails that use internal distraction mechanisms, thereby eliminating the need for external fixation entirely, are now available for clinical trials in Europe.[26] The use of an IM nail for bone transport instead of an external fixator facilitates early full joint motion and alleviates pin site complications. Patient satisfaction and quality of life during and after the transport procedure favors the use of IM bone transport. Delayed healing of the docking sites or regeneration are easily managed with simple exchange nailing. These devices will certainly add a new tool for the treatment of traumatic bone defects.

Infected Bone Defects: State-of-the-Art Treatment

Infected bone defects represent one of the most difficult and challenging conditions to treat in orthopaedic trauma.

Successful treatment requires appropriate preoperative workup and a staged approach to surgical management. Preoperative workup should consist of imaging studies, white blood cell counts, erythrocyte sedimentation rate, and C-reactive protein. In addition, patients should be investigated and treated where possible, for any nutritional or metabolic deficiencies, immune compromise and other comorbidities impacting healing. The initial surgical stage is focused on eradication of infection with a combination of surgical and antibiotic treatment. Several goals exist for the initial stage of surgery:

1. Removal of all loose or chronically infected hardware,
2. Debridement of all infected or nonviable bone and soft tissue,
3. Multiple deep tissue biopsies for culture and sensitivity to guide antibiotic treatment (minimum of 3–5 specimens),
4. Revision of fracture fixation (using either temporary or permanent fixation),
5. Placement of local antibiotic treatment,
6. Soft tissue management as required (eg, primary closure, vacuum-assisted closure, or flap coverage).

Several options exist for revision fracture fixation including both temporary methods such as external fixation, antibiotic nails, cast immobilization, and permanent methods such as plate fixation, IM nailing, and locked antibiotic nailing (see **Fig. 2**, **Supplemental Digital Content 2**, http://links.lww.com/JOT/A297).[25,27,28] Similarly, several options exist for local antibiotic treatment including antibiotic coated nails (see **Fig. 2**, **Supplemental Digital Content 2**, http://links.lww.com/JOT/A297), antibiotic impregnated osteoconductive pellets (eg, *Osteoset T*, Wright Medical, Memphis, and TN), antibiotic powder, antibiotic cement beads, and antibiotic cement spacers in combination with the induced membrane technique (see **Fig. 3**, **Supplemental Digital Content 3**, http://links.lww.com/JOT/A298).[11,27,29] These demonstrate a large bone defect (approximately 13 cm) and the membrane formed around the spacer (yellow arrow). RIA bone graft was combined with morselized cancellous allograft and BMP-2 (note: this is an off-label indication for BMP-2). (J and K) Follow-up radiographs 9 months following bone grafting demonstrating healing and synostosis between the tibia and fibula. Unfortunately, there is a distinct lack of evidence regarding the different options for either fixation or local antibiotic treatment, and most of the literature to date has consisted of level 4 retrospective series. In one of the few level 1 studies in this area, McKee et al reported on a small prospective randomized trial of 30 patients with chronic osteomyelitis and/or infected nonunion treated with surgical debridement and antibiotic-impregnated bioabsorbable bone substitute (*Osteoset T* = tobramycin-impregnated medical-grade calcium sulfate) or antibiotic PMMA cement beads.[29] Both groups had high rates of infection eradication and fracture union, however, there were more reoperations in the PMMA group (15 vs. 7, $P = 0.04$).

After the initial surgical stage, the patient is treated with culture-specific antibiotics and followed clinically and serologically for resolution of infection. Once infection is eradicated on this basis, the second surgical stage consists of definitive fracture fixation (if temporary fixation was used in the initial stage) and reconstruction of the bone defect. Reconstruction of bone defects can be achieved with a variety of strategies including the following: autogenous iliac crest bone grafting, RIA bone grafting, bone graft substitutes, bone transport techniques, or any combination of these.[1,11,25,28] As alluded to above, not all bone defects are created equal, and some bone defects may heal spontaneously with revision fixation and eradication of infection, depending on their size, location, the soft tissue environment, and patient factors (see **Fig. 2**, **Supplemental Digital Content 2**, http://links.lww.com/JOT/A297). For those patients who require a second stage to reconstruct the bone defect, there is once again a paucity of evidence for 1 treatment strategy over another and the literature has consisted primarily of level 4 studies; therefore, treatment selection can be based on the characteristics of the bone defect (size, location, soft tissue environment, etc) and the available expertise/resources and surgeon/patient preferences (see **Fig. 3**, **Supplemental Digital Content 3**, http://links.lww.com/JOT/A298). It is important to note that many of these series have reported relatively high levels of treatment success when the above treatment algorithm is followed.

CONCLUSIONS

Bone defects continue to represent a significant burden of disease and their treatment remains difficult. High-level evidence to define what constitutes a critical-sized bone defect and to guide management is lacking. At the present time, treatment should be individualized, with adherence to the principals outlined above and a firm comprehension of the available options. Clearly, further research in this area is required to increase our understanding and improve treatment outcomes.

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