Current Concepts Review

Modern Management of Severe Open Fractures of the Extremities

The Role of the Induced Membrane Technique

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- The administration of antibiotics, revascularization, effective initial debridement, stabilization, and dead-space management are important time-dependent, acute actions.
- Following the adequate resuscitation of the patient and the local soft tissues, the first stage of the Masquelet technique is performed together with the definitive coverage of the soft-tissue defect.
- The optimal time for the second stage (grafting of the bone defect) depends on the progress of the soft-tissue reconstruction and the overall state of the patient. It is usually at 6 to 14 weeks.
- Bone graft involves cancellous autograft; depending on the volume of the defect, it can be acquired using different donor sites and methods and can be combined with cancellous allograft, bone substitutes, bone marrow aspirate, and inductive molecules.
- Bone healing is independent of the size of the defect, assuming that revascularization of the graft material has not been disturbed.
- The development of signs of a fracture-related infection in the clinical setting of a severe open fracture dictates surgical treatment and pathogen-specific antibiotics, debridement of the membrane and the surrounding soft tissues, and reinitiation of the staged process of limb salvage.
- The results of staged management of severe open fractures with bone defects are reproducible and good.

Open fractures are complex injuries in which the soft-tissue envelope surrounding the fracture is breached. These injuries are a source of significant morbidity, with evidence of greater deterioration of the patient's quality of life than after a stroke[1]. The incidence of open fractures in the United Kingdom has increased, from 2.5 per 100,000 person-years in 2008 to 7.03 per 100,000 person-years in 2019[2]. Open fractures most often affect men in their third decade, most commonly following a road traffic collision (43% of cases)[2]. The most frequently affected bones include a finger phalanx, the tibia, and the distal radius[3]. In 80% of cases, the patient presents with an isolated limb injury; however, 20% of patients have other injuries[2]. For 4 decades, open fractures have been classified with the Gustilo-Anderson system[4]. Some newer classification strategies attempt to include the associated factors most relevant to the final outcome (i.e., host profile, bone loss, skin coverage, and musculotendinous and

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nerve tissue trauma)[5,6]. Others attempt to simplify the categorization of the presenting open fractures, promoting the initial triage of the complex ones to units with the appropriate readiness and expertise to address both the skeletal component of the injury as well as the soft-tissue defect in a timely manner[7,8].

A critical-sized bone defect has been traditionally defined as involving >50% of the cortical diameter in a segment >1 cm long, but this is not universally accepted[9]. The Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) defined a critical-sized bone defect in the tibia as a defect of >1 cm affecting >50% of the cortical circumference. However, defects of this size were later demonstrated to heal without intervention in 47% of cases[9,10]. Sanders et al. suggested that a critical-sized bone defect should instead be defined as one affecting >50% of the cortical diameter in a >2-cm-long segment[10]. Bone defects have been classified using different systems that take into account the extent and location of the bone loss[11] or even soft-tissue and host characteristics[12]. Critical-sized defects occur in 11% of Gustilo-Anderson grade-III injuries, drastically increasing the complexity of an attempted limb salvage[13]. The extension of the OTA/AO open fracture classification system also describes the presence of a bone defect well, taking into account its size and shape[14]. It has been validated and found to be easily applicable using radiographs and to have substantial intraobserver and interobserver agreement[15].

Management Options for Acute Bone Loss

The tibial bone remains the most common site of long-bone open fractures with bone loss (68% of cases), followed by the femur (22% of cases)[9]. According to the Ferreira and Tanwar classification system[12], fixation of type-1 defects (≤20 mm) can be followed by secondary bone grafting if spontaneous healing does not occur. Shortening of ≤20 mm in the lower limb is well tolerated and has the advantage of potentially downgrading the soft-tissue defect to obviate the need for soft-tissue reconstruction[16,17]. In bone defects involving the full circumference in high-functioning, type-A hosts (in whom acute shortening without relengthening would not be considered), the defect is usually managed with the Masquelet induced membrane technique (MIMT) or with distraction osteogenesis.

In contrast, shortening of >20 mm is generally poorly tolerated, and, type-2, 3, and 4 defects therefore require bone-length reconstruction or occasionally lead to an amputation. In a comparative study, Tetsworth et al.[18] identified slightly better results and fewer complications after acute shortening or lengthening in comparison with bone transport for defects of <50 mm. The MIMT can similarly be used in this situation, with fixation achieved with an intramedullary device in the diaphysis, a peri-articular plating system in the metaphysis, or an external fixator if the soft-tissue envelope is of poor quality.

Type-3 defects are considered massive defects requiring specialist expertise. The MIMT can again be utilized to manage these defects, although additional concerns relevant to the provision of large volumes of bone graft require careful consideration. In these circumstances, graft expansion techniques are utilized, with allograft or synthetic bone substitutes added to the autograft at a ratio below 1:3[12]. Concerns have previously been reported with regard to the inability to lengthen a shortened limb with this technique, and, therefore, it is imperative to attain the correct limb length at the index procedure[19].

The Ilizarov technique, applied by specialist limb-reconstruction surgeons, is well documented to obtain high union rates and few treatment failures, especially for defects of >6 cm, and a mean external fixation index of 1.7 months/cm[20]. Treatment can be accelerated through the use of bifocal or trifocal lengthening[21]. Transport over a nail can similarly be utilized to reduce the external fixator time and pin-site problems and to promote function[22,23]. Lengthening nails and plate-assisted bone segment transport are also gaining popularity, demonstrating similar consolidation indices to external fixation-based techniques[24-26]. Vascularized bone grafting is used for type-3 bone defects but with the additional donor-site morbidity secondary to harvesting the graft[27]. However, there is no conclusive evidence comparing the different treatment methods of acute bone loss.

Type-4 defects are associated with protracted treatment times and a high rate of complications. The MIMT remains an option, and it has a theoretical advantage in that the consolidation time (which is an important factor, especially for large defects) is independent of the size of the defect. Custom 3-dimensionally printed cages have recently been introduced to assist in the containment and remodeling of the bone graft at the second stage[28]. Bone transport is also commonly practiced but is associated with extended periods of treatment, high costs, and higher rates of problems[29-32]. All 3 of these issues can be reduced through the use of multifocal transport as well as bone transport followed by internal fixation. Bone transport and the MIMT can be combined, transporting through the membrane. In a recent randomized controlled trial, this combination resulted in significantly fewer docking site nonunions and fewer recurrent infections compared with bone transport alone[33]. The regenerate bone following distraction osteogenesis is histologically indistinct from the adjacent normal bone, whereas the remodeling and maturation of the grafted defect area of the MIMT method depends on the fixation method. Especially when bridging plates are used, the graft material never fully remodels, does not reconstitute the medullary canal, and remains radiographically distinct from the adjacent normal bone[34].

Vascularized fibular grafts are again possible in this patient population, although the patient will need to undergo a prolonged period of limited weight-bearing while graft hypertrophy occurs, and the reported graft fracture rate is 30%[35]. The use of structural allografts for the reconstruction of acute bone loss has also been described in recent publications, with successful results[36,37].

The MIMT[34,38,39] for acute traumatic defects usually follows the initial damage control resuscitation phase. Primary irrigation and debridement and temporary fixation, with additional revascularization and fasciotomies, precede the first stage of the MIMT in the most severe of the cases. The second stage is usually performed 6 to 14 weeks later, following successful soft-tissue reconstruction, resolution of the localized inflammatory reaction, and establishment of the membrane and its accompanying vascularity[40,41].

TABLE I Injury Characteristics of Patients Undergoing Combined Fixation and Soft-Tissue Reconstruction*

Study	Study Design	No. of Patients	Site	Gustilo-Anderson Grade	Timing of Soft-Tissue Reconstruction	Type of Soft-Tissue Reconstruction	Definitive Fixation
Kuripla[78] (2021)	Retrospective multicenter case series	260	Tibia: 260	III: 260	NR	Fasciocutaneous: 47 Rotational: 136 Free muscle: 118	IM nail: 193 Plate: 67
Aljawadi[75] (2022)	Prospective single-center case series	120	Femur: 2 Tibia: 72 Ankle and pilon: 31 Foot: 10 Multiple: 5	IIIB: 120	Mean time, 7.7 days (range, 1 to 30 days) Fix and flap in same session	Skin grafting: 21 Rotational flap: 46 Free muscle: 53	Plate: 43 IM nail: 29 Circular frame: 21 Monolateral external fixator: 8 Hybrid techniques: 19
Singh[82] (2020)	Retrospective single-center case series	33	Tibia: 33	IIIB: 15 IIIC: 18	Fix and flap in <72 hours in all	Local rotation: 4 Free fasciocutaneous: 5 Free muscle: 24	Uniplanar external fixator: 14 Multiplanar external fixator: 19
Liu[73] (2023)	Retrospective single-center case series	244	Tibia: 132 Foot and ankle: 112	II: 38 IIIA: 61 IIIB: 80 IIIC: 65	<3 days: 67 3 to 7 days: 96 >7 days: 81	Free muscle: 244	NR
Zelenski[74] (2023)	Retrospective single-center case series	118	Tibia: 118	IIIA: 13 IIIB: 96 IIIC: 7†	NR but categorized as <4, 4 to 10, and >10 days	Local fasciocutaneous: 10 Local myocutaneous: 42 Free fasciocutaneous: 5 Free muscle: 61	Nail: 48 Plate: 47 External fixation: 19†
Cao[76] (2022)	Retrospective single-center case series	394	Tibia: 394	IIIB: 394	Early (167): mean, 6.15 days Late (227): mean, 16.46 days	Free muscle: 394	NR
Lee[79] (2021)	Retrospective single-center case series	46	Tibia: 46	III: 46	Mean, 18.8 days	Free muscle: 46	NR
Pincus[81] (2019)	Retrospective multicenter cohort study	454	Tibia: 246 Ankle: 171 Tibia and ankle: 37	III: 454	Early (227): 4 days Late (227): 12 days	NR	Internal fixation: 400 External fixation: 54
Mathews[80] (2015)	Retrospective single-center case series	73 (74 patients)	Tibia: 74	IIIA: 5 IIIB: 66 IIIC: 3	Fix and flap: 48 Delayed reconstruction: 26	Direct closure: 5 Amputation: 6 Split skin graft: 3 Local flap: 18 Free flap: 42	NR
Chua[77] (2014)	Retrospective single-center case series	89	Tibia: 89	IIIB: 81 IIIC: 8	<72 hours: 30 >72 hours: 59	Local fasciocutaneous: 14 Local muscle: 36 Free muscle: 39	External fixation: 32 IM nail: 24 Plate: 25 Circular frame: 6 Cast: 1 Not specified: 1

*NR = not reported, and IM = intramedullary. †In the original study, there is a reference to 118 overall tibial fractures. There is a record on the type of open fracture per the Gustilo-Anderson classification for 116 of the fractures and on the mode of fixation for 114 of the fractures.

Phase 1: Initial Assessment and Management

Patients could be managed in multiple stages mostly because of the presence of persisting hemodynamic instability or other severe associated injuries. Physiologically stable patients could also be managed in multiple stages because of the severity of the local soft-tissue and osseous tissue trauma and the complexity of the clinical problem (musculoskeletal temporary surgery [MuST])[42].

Initially, the patient is managed according to the Advanced Trauma and Life Support (ATLS) principles, with the limb

TABLE II Outcomes of Patients Undergoing Combined Fixation and Soft-Tissue Coverage*

Study	Follow-up	Union Rate	Time to Union	Complications	Secondary Procedures
Kuripla[78] (2021)	Min., 12 mo	NR	NR	Infection: 32.4% Mean time from injury to coverage: 18.4 days in infected group, 10.2 days in non-infected group	Flap failure requiring revision or amputation: 16.1%
Aljawadi[75] (2022)	25 mo (range, 12 to 45 mo)	86.7%	32 wk (range, 15 to 73 wk)	Flap complication: 36 Delayed union or nonunion: 17 Superficial infection: 32 Deep infection: 3	Autologous BMAC injection: 10 Revision for nonunion: 3 (2 in infected group) Revision for infection: 1 Amputation: 3 Flap-related procedure: 6
Singh[82] (2020)	Min., 36 mo	45%	35 wk	Flap failure: 9% Superficial infection: 24% Deep infection: 12% Malunion: 9%	Secondary procedure to achieve union: 55% Secondary stabilization procedure: 48% Debridement of pin sites: 6% Debridement and bone transport for infection: 6%
Liu[73] (2023)	NR	NR	NR	Flap necrosis: 13% overall but varied according to time to treatment: <3 days, 3% 3 to 7 days, 9% >7 days, 26%	NR
Zelenski[74] (2023)	60 mo	69%	129.9 days	Nonunion: 31% Higher nonunion rate with early coverage, and with fasciocutaneous flaps Osteomyelitis: 17%	Flap salvage: 2 Flap revision: 48 Second free flap: 23 Nonunion procedure: 31 Amputation: 11
Cao[76] (2022)	Min., 24 mo	97%	Early coverage: 5.7 mo Late coverage: 9.1 mo	Overall complication rate: 4.2% with early coverage, 11.5% with late coverage Chronic infection: 8% (80% in late group) Flap complications: 12% (76% in late group)	Nonunion procedure: 5 Bone defect procedure: 6 Flap revision procedure: NR
Lee[79] (2021)	NR	NR	NR	Flap-related complications: 34.8%, increased if flap delayed >33 days Osteomyelitis: 21.7% Flap complications increased Fracture complications increased if flap delayed >91 days	NR
Pincus[81] (2019)	NR	NR	NR	Deep infection: 2.2% in early group, 8.4% in late group Amputation: 5.3% in early group, 8.4% in late group Pneumonia: 2.6% in early group, 7.1% in late group Decubitus ulceration: 0.9% in early group, 6.2% in late group	NR

continued

TABLE II (*continued*)

Study	Follow-up	Union Rate	Time to Union	Complications	Secondary Procedures
Mathews[80] (2015)	Min., 1 yr	NR	NR	Deep infection: 4.2% for fix and flap, 34.6% for staged coverage No difference in infection with coverage <72 hr	NR
Chua[77] (2014)	23 mo	53%	Early coverage, 12.5 mo Late coverage, 13.9 mo	Superficial infection: 3% in early group, 9% in late group Deep infection: 23% in early group, 54% in late group Flap failure: 20% in early group, 9% in late group	Secondary procedure to achieve union: 47% in early group, 42% in late group Amputation: 4 cases (all late group)

*NR = not reported, and BMAC = bone marrow aspirate concentrate.

given a lower priority unless it is the source of a major arterial bleed. After the primary survey and resuscitation, the focused examination of the limb includes careful assessment and detailed documentation of its neurovascular status. In the rare occasion of severe hemorrhage from the limb, direct pressure and/or application of a tourniquet at the pre-hospital phase and early involvement of a vascular surgeon are crucial. Prompt identification of hard signs of ischemia (lack of pulses, continuing blood loss, or an expanding hematoma) or, if in doubt, emergency diagnostics (computed tomography [CT] angiography or intraoperative angiography) and restoration of blood flow (temporary shunting, graft reconstruction, or vessel repair), optimally within 3 to 4 hours, are essential for the survival of the limb[43,44].

If not already administered in the pre-hospital setting, antibiotics should be administered as early as possible, ideally within the first hour[45]. Tetanus prophylaxis should also be provided as soon as is feasible. Contemporary infection prevention strategies indicate that monotherapy with a broad-spectrum antibiotic (intravenous cephalosporins or amoxicillin-clavulanate) suffices[46]. The addition of aminoglycosides in multitherapy protocols has been associated with increased risk of acute kidney injury without significant benefits regarding the prevention of infection[47]. Ceftriaxone has recently been found to be advantageous for severe open fractures compared with cefazolin, because of its pharmacokinetics (a single dosage per day) and adequate spectrum of coverage as a single agent[48]. Shorter courses (≤72 hours) of prophylactic antibiotics have been proven to generally be equally effective compared with extended ones[49,50], with lower odds of fracture-related infections only found in the subgroup with severely contaminated wounds when extended use of antibiotics (>72 hours) was practiced[51].

Gross debris and contamination should be removed before coverage of the wound with a saline solution-soaked gauze dressing. The wound of the open fracture should be photographed to avoid repeated exposure and secondary in-hospital contamination. With appropriate analgesia, the limb should be aligned and supported with a splint.

In the presence of marine, agricultural, or sewage contamination, emergency irrigation and surgical debridement is required as soon as possible, together with enhanced early antibiotic coverage (addition of anaerobe antimicrobials to the prophylactic antibiotic course)[52]. Contemporary evidence supports the urgent primary surgical debridement of high-energy open fractures within 12 hours and of lower-energy ones within 24 hours[53,54]. Both the LEAP (Lower Extremity Assessment Project)[55] and FLOW (Fluid Lavage of Open Wounds) studies[56,57] highlighted that increasing time to the first debridement did not independently increase the risk of infectious complications or reoperations. Effective debridement starts with generous longitudinal extension of the traumatic wound, continuous with the systematic debridement from superficial to deep and from the periphery to the center, including the medullary canal, with removal of nonviable tissue. The preservation of neurovascular bundles, tendons, and articular surface fragments is important[58].

Irrigation should be performed with large volumes of warmed normal saline solution via gravity drainage[59]. High-pressure pulsatile lavage could damage already injured tissues and could drive bacterial contamination into deeper layers[60,61], and given that no clinical benefit was seen in the FLOW trial, its use should be avoided[62]. Surfactants also failed to demonstrate any clinical benefit, and antiseptic solutions may have a damaging effect on both skin and bone and therefore are generally avoided[63].

Given concerns for tissue penetration by systemic antibiotics in a severely injured limb, the use of local antibiotics is advocated, reducing the risk of fracture-related infection by 11.9%[64]. The delivery of local antibiotics can involve the use of an antibiotic bead pouch, of antibiotic-impregnated polymethyl methacrylate (PMMA) cement spacers, or of absorbable carriers[64,65]. These methods also help in the direction of effective dead-space management.

If soft-tissue coverage can be achieved, the fracture should be definitively stabilized, provided that the general state of the injured patient allows that. If the above conditions are not met, then a temporary bridging fixator should be applied, with a plan

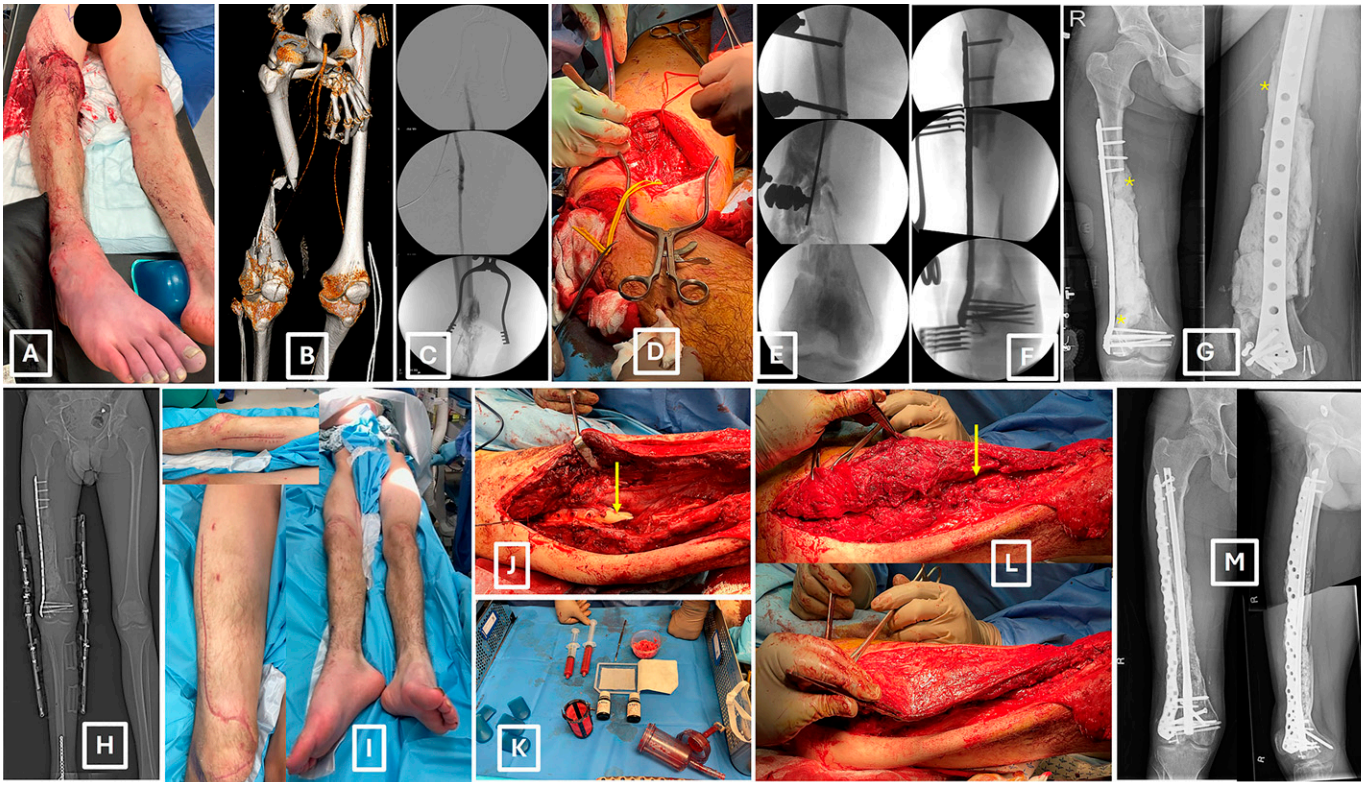

Fig. 1

Case 1. An 18-year-old man with an open, grade-IIIC, right femoral fracture, resulting in a bone defect with a length of 21 cm, following an e-scooter accident. **Figs. 1-A through 1-E** Phase 1: The initial assessment and management. **Fig. 1-A** Clinical photograph at the emergency department, showing a 6-cm dorsomedial open wound at the distal femur. The leg had warm ischemia for 1.5 hours after the injury. **Fig. 1-B** Three-dimensional CT angiography reconstruction showing a missing diaphyseal segment, metadiaphyseal and intra-articular comminution, and an intimal tear of the superficial femoral artery. **Fig. 1-C** Intraoperative angiography showing the superficial femoral artery injury and a pulseless distal segment. **Fig. 1-D** Clinical photograph during superficial femoral arteriotomy and direct repair with a greater saphenous vein patch, following a medial approach to the artery and initial shunting of the artery defect. **Fig. 1-E** Knee-bridging external fixation, irrigation, debridement, and insertion of a temporary PMMA spacer with antibiotics into the defect. **Figs. 1-F and 1-G** Phase 2: First stage of the Masquelet technique 48 hours later. **Fig. 1-F** Fluoroscopic images following anatomic reduction of the articular segment, subsequent bridge-plate fixation of the femur, and after insertion of a PMMA spacer with vancomycin and gentamycin that overlaps the main fragment ends (yellow asterisks in Fig. 1-G), following the principles of the first stage of the Masquelet technique. All wounds were closed primarily at this stage without the need for plastic surgical reconstruction. **Fig. 1-G** Postoperative radiographs of the end construct following the completion of the first stage. **Figs. 1-H and 1-I** Phase 3: Interim period. **Fig. 1-H** CT scanogram made as part of the alignment investigations during the interim period before the second stage. **Fig. 1-I** Clinical photographs showing clinically evident external rotation of the right leg by 23° in comparison with the left side and shortening of 2.5 cm. The surgical incisions and initial wound apparently healed well without any signs of a fracture-related infection. **Figs. 1-J through 1-M** Phase 4: Second stage of the Masquelet technique 8 weeks later. **Fig. 1-J** Clinical photograph showing an extended lateral approach following the removal of the initial bridging plate (to allow the correction of the rotational deformity), a longitudinal incision of the induced membrane, and the removal of the cement spacer. The yellow arrow points to the nonviable bone-end proximally (potentially a result of overheating at the first stage and being inert during the interim period) that requires further debridement. **Fig. 1-K** Clinical photograph of the components of the composite graft, which, in this case, include the RIA autologous graft from the contralateral femoral canal, osteoconductive bone substitute, bone marrow aspirate concentrate, and a collagen sponge containing bone morphogenetic protein (BMP)-2. **Fig. 1-L** Clinical photographs of the final closure of the lateral surgical wound. In the upper photograph, the yellow arrow points to the sutured and closed induced membrane. The lower photograph shows the coverage of the defect with the bulk of the preserved vastus lateralis. **Fig. 1-M** Latest follow-up radiographs of the femur 6 months after the second stage, showing the nail-plate bridging construct and clear evidence of graft integration and remodeling.

made to return to the operating room for definitive fixation and soft-tissue reconstruction. In this setting, the soft-tissue defect can be managed with a negative-pressure wound therapy system, although that was proven inferior to an antibiotic bead pouch with respect to the prevention of infection[65] and was associated with a low probability of cost-effectiveness in comparison with standard dressings according to the WOLLF (Wound management of Open Lower Limb Fractures) trial[1,66].

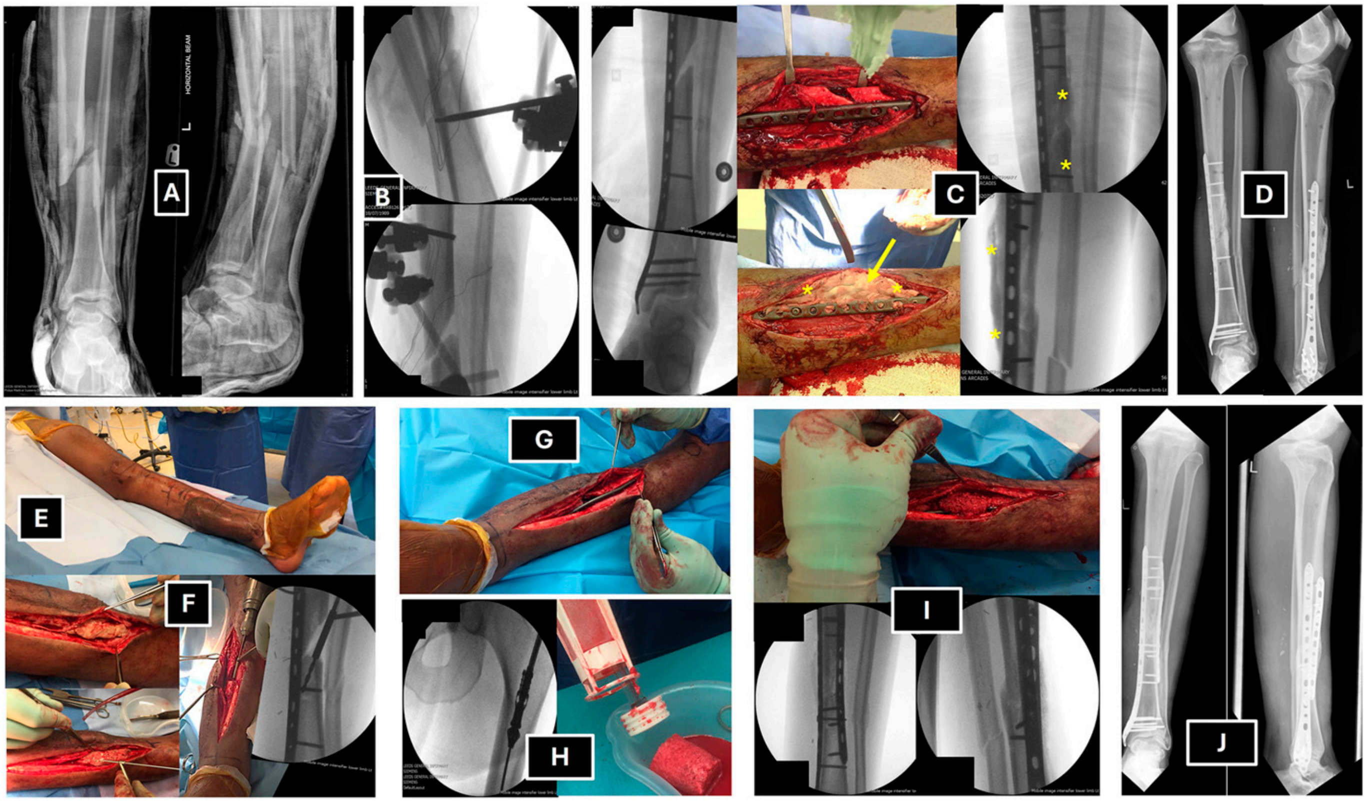

Fig. 2

Case 2. A 27-year-old man with an open grade-IIIB midshaft left tibial fracture, resulting in a triangular defect with a maximum length of 6 cm, following a fall in a river. **Figs. 2-A and 2-B** Phase 1: Initial assessment and management. **Fig. 2-A** Radiographs of the left tibia on presentation after coverage of the wound and splinting of the extremity. **Fig. 2-B** Radiographs showing the MuST surgical strategy, with urgent initial debridement (3 detached butterfly fragments were removed) within 4 hours of the accident (the wound was considered highly contaminated and was covered prophylactically with intravenous amoxicillin-clavulanate and metronidazole), local antibiotics (gentamycin beads), bridging external fixation, and application of a negative-pressure wound therapy system. **Figs. 2-C and 2-D** Phase 2: First stage of the Masquelet technique, definitive fixation (bridge plating), and soft-tissue definitive management (free gracilis flap and split skin graft), representing a fix-and-flap strategy at 72 hours. **Fig. 2-C** Fluoroscopic images and clinical photographs showing the osseous defect in the lateral midshaft region of the left tibia bridged with a medial periarticular distal locking plate. The yellow arrow indicates the cement spacer at the region of the defect. The yellow asterisks in the fluoroscopic images at the right and in the lower clinical photograph indicate where the spacer overlaps the ends of the main fragments. **Fig. 2-D** Postoperative radiographs following the first stage, with the patient starting very early full weight-bearing and functional rehabilitation of the knee and ankle, following the first 6 days of observing the good recovery of the microsurgical free flap. **Fig. 2-E** Phase 3: Interim or latency period. Clinical photograph showing the good healing of the free flap and the absence of any signs of a fracture-related infection. **Figs. 2-F through 2-J** Phase 4: Second Masquelet stage at 8 weeks after the injury. **Fig. 2-F** The top left clinical photograph shows the induced membrane (held with forceps after its longitudinal incision) after the cautious dissection of the free flap away from its pedicle. The bottom left clinical photograph illustrates the drill-holes made in the cement spacer to allow its removal from the defect in pieces to minimize any risk of damaging the induced membrane. The membrane from the medullary canal was then removed and communication of the medullary canal with the defect was restored with a drill-bit and curettage, as shown in the right-hand clinical photograph and fluoroscopic view. **Fig. 2-G** A second plate was inserted laterally to augment the fixation and allow the patient to continue postoperatively unrestricted weight-bearing. **Fig. 2-H** Fluoroscopic view of the autologous bone harvesting from the ipsilateral femur using the RIA system, and clinical photograph of the large volume of autologous bone obtained on this occasion. No further expansion was required of the graft volume was required in this case as it was considered adequate to cover the defect. **Fig. 2-I** Clinical photograph and fluoroscopic views showing the grafted defect prior to closure of the membrane. **Fig. 2-J** Final radiographic follow-up 9 months since the injury. The patient was fully mobile and had no signs of fracture-related infection or other secondary complications.

Phase 2: First-Stage Masquelet Technique and Soft-Tissue Reconstruction

Following the initial phase consisting of successful resuscitation of the patient and/or the extremity, the surgical team plans the definitive management of the soft-tissue defect, the definitive stabilization of the fracture, and the reconstruction of the bone defect. The aim should be to provide, optimally during a single session, the definitive fixation of the fracture and the provision of a viable soft-tissue cover, a practice that reduces the risk of fracture-related infection[67]. When definitive soft-tissue coverage is delayed, especially when internal fixation has been performed, post-debridement cultures have been shown to help to guide the timing of flap coverage and further management according to the published protocol of Lenarz et al.[68].

Preoperative planning includes CT angiography to assess the remaining blood supply of the injured extremity, and to plan the anastomosis of a microsurgical free flap if that is required[69,70].

The timing of this phase has been debated and studied over the last 2 decades and is dictated primarily by the state of the patient and secondarily by the available resources and expertise.

Early soft-tissue microvascular reconstruction (within 72 hours of the injury) is associated with accelerated times to union, lower infection rates, and fewer free flap failures[71]. The concept of "fix and flap" was suggested as a strategy to reduce infection rates as well as the number of surgical procedures. Gopal et al. demonstrated that this combination was feasible and safe in a specific setup involving a tertiary referral hospital with high levels of readiness of the surgical team[72]. Lately, studies have examined the impact of the timing of soft-tissue reconstruction on the rates of flap failure, fracture-related infection, and nonunion (Tables I and II)[73-82]. Current evidence suggests that "fix and flap" is a safe and effective technique that can be employed early in the patients' journey[8,80,83]. In the study by D'Alleyrand et al.[83], after controlling for known risk factors for complications and infection, a logistic regression model identified no increased risk of those 2 outcomes for "fix and flap" procedures within the first 7 days after the injury, whereas the odds increased by 11% for complications and 16% for infection for each day beyond day 7 ($p < 0.04$)[83]. In a recent retrospective study, the time from definitive fixation to flap coverage was most predictive of subsequent wound infections, suggesting the avoidance of definitive internal fixation before effective soft-tissue coverage[78]. Newer alloplastic subdermal replacement grafts, together with simple skin grafting, have been utilized successfully for closure of critical-sized wounds[84,85].

When the size of the soft-tissue defect was assessed as an independent risk factor, it was found that a wound size of >200 cm^2 was 3 times more likely to lead to wound complications ($p = 0.04$) after adjusting for factors such as the severity of contamination and type of wound closure[86].

Further debridement of the bone defect zone is performed to leave healthy, viable bone ends across the defect. Soft tissues are also debrided and irrigated pending the soft-tissue reconstruction of a "living wound."[87]

Prior to the soft-tissue reconstruction and final wound coverage, the fracture is fixed with a bridging internal fixation construct (nail or plate). Plating constructs offer optimal control of periarticular comminution and better rotational stability but require more bone graft to fill the bone defect and are associated with more incidents of fatigue failure due to being off-axis and being load-bearing implants. Intramedullary devices offer mechanical advantages (an in-axis load-sharing mechanical environment), requiring less bone graft volume at the second MIMT stage. The current understanding regarding fixation device options is that intramedullary nailing has certain advantages over bridge plating, including the need for a smaller volume of bone graft at the second stage, less frequent need for secondary grafting procedures (10.5% compared with 28.1%), fewer reoperations in general (17.5% compared with 46.9%), and less time to full weight-bearing (2.44 compared with 4.63 months), as reported by Morwood et al.[88].

External fixators as a definitive fixation method for acute traumatic bone defects treated using the MIMT are rarely used currently, although they were used frequently by Masquelet in the original series[38,89].

The PMMA spacer is mixed with added antibiotics; usually 3 to 4 g of vancomycin powder and 2.4 g of tobramycin powder are added to 40 g of PMMA cement, or vancomycin only is added to PMMA preloaded with 500 mg of gentamycin (PALACOS G; Zimmer Biomet) to maximize its porosity, as previously reported[38,39]. The original description of the technique by Masquelet suggested the use of a PMMA spacer without antibiotics[34]. However, most recent clinical series have used antibiotic-loaded spacers during stage 1, with the high local concentrations of antimicrobials being beneficial in heavily contaminated wounds[90] and having a neutral[38] or even beneficial impact on the quality of the created induced membrane[91,92]. The spacer should overlap the bone ends of the main fragments by 10 to 20 mm, to allow the uniform development of the induced membrane in continuity with the periosteum of the bone ends. Surrounding soft tissue and vulnerable neurovascular structures should be protected during the exothermal setting of the cement spacer (using saline solution irrigation or a cold saline solution-soaked swab)[38,39].

Whenever the definitive wound coverage is not possible at the same session or it fails, the PMMA-antibiotic spacer should be replaced and a repeat debridement should be performed at the time of further plastic surgical or microsurgical reconstruction[39].

Phase 3: Interim Period

In the first days of this phase, the focus is on optimizing the conditions for the survival of the soft-tissue reconstruction. In general, this phase lasts for about 5 to 7 days and, subsequently, the patient is allowed to bear weight and initiate range-of-motion exercises of joints adjacent to the fracture.

Close monitoring for any signs of fracture-related infection is performed, and initial radiographs are made[93,94]. Careful radiographic assessment of the alignment and the length of the extremities should be performed[95], as revision of the fixation is feasible, and may be required, at the second stage of the MIMT (Fig. 1).

The timing of the second-stage surgery has been debated over the last decade. In cases of acute bone loss, this timing is dependent mostly on the state of the soft tissues and the absence of signs of a fracture-related infection. The patient should not have taken any antibiotics for at least 2 weeks, to

TABLE III Series Presenting Use of the Masquelet Technique in the Acute Trauma Setting*

Study	Acute Cases	Anatomical Site(s)	Soft-Tissue Reconstruction	Mean Defect Size	Gustilo Classification	First-Stage Fixation Method	Mean Time to Second Stage
Steffenson[110] (2023)†	127	Tibia and femur	NR	DIM: 5.74 cm MIM: 6.47 cm	NR	IM fixation:48 Plate fixation: 68	14.6 wk
	69	Tibia	NR	DIM: 5.34 cm MIM: 4.54 cm	II: 6 IIIA: 28 IIIB: 26 IIIC: 3	Unable to establish	NR
	51	Femur	NR	DIM: 6.76 cm MIM: 8.35 cm	II: 5 IIIA: 35 IIIB: 0 IIIC: 1	Unable to establish	NR
Lan[109] (2022)	17/44 MT‡	Tibia	Local flap: 3 Free flap: 14	5.1 ± 1.6 cm	IIIA: 2 IIIB: 7 IIIC: 8	External fixation	6 to 8 wk
Kasha[108] (2019)	27	NR	NR	NR	NR	NR	NR
	1	Femoral shaft	NR	6 cm	NR	External fixation	48 days
	14	Distal femur	Skin graft: 4 Flap: 2	7.1 cm (range, 5 to 10 cm)	NR	External fixation: 4 Plate: 10	42.5 days
	6	Proximal tibia	Skin graft: 3 Flap: 6	5.3 cm	NR	External fixation: 2 Plate: 4	41.8 days
	1	Tibial shaft third	As above	6 cm	NR	External fixation	38 days
	2	Tibial distal third	As above	3.5 cm	NR	External fixation: 2	42 days
	2	Humerus	Skin graft: 1	4 cm	NR	Plate: 2	49 days
	1	Ulna	Skin graft: 1	4 cm	NR	Plate: 1	40 days

*NR = not reported, DIM = diaphyseal induced membrane, MIM = metaphyseal induced membrane, IM = intramedullary, ORIF = open reduction and internal fixation, RIA = Reamer-Irrigator-Aspirator, ICBG = iliac crest bone graft, AC = allograft chips, BMP = bone morphogenetic protein, and MT = Masquelet technique. †The results of this retrospective cohort study of 4 Level-I centers can be explained by the delayed first-stage procedure (within 3 weeks after the injury) in contrast to the protocol described in this article. ‡The remaining patients in the cohort underwent a free vascularized fibular graft.

minimize the chance of false-negative deep tissue samples at the time of the second stage. Although the peak of biological activity of the induced membrane has been found to be around the fourth week[96], the majority of clinical evidence points toward an optimal interim period of 6 to 14 weeks. By this time, the soft tissues have been seen to have settled, and the induced membrane appeared thicker but still possessed strong osteoinductive and angiogenic properties[38,41,97]. Some authors have advocated scraping or pie-crusting of the inner layer of the membrane in more delayed second stages to induce local neovascularization[98].

Phase 4: Bone-Grafting Second Stage of the Masquelet Technique

The second-stage approach needs to be planned carefully, often together with the originally involved plastic surgeon, in order to protect the vascular pedicle of the microsurgical reconstruction. The membrane is incised longitudinally and the cement spacer is carefully removed, preserving the induced membrane. The membrane is removed only from inside the medullary canal, which restores the communication of the medullary canal with the grafted defect. In a diaphyseal segment, the canal can be debrided with a hand reamer, and a curet is utilized to stimulate bleeding (when the fixation construct is not a nail)[38,39].

The bone ends are re-debrided for a few millimeters until bleeding bone is encountered (fragment ends become nonviable because of the exothermic reaction of the cement in stage 1 and being inert over the interim period). Multiple deep-tissue samples are taken and are sent for histopathologic and microbiologic testing[99]. If the membrane appears macroscopically infected, the membrane, soft tissues, and bone ends should be debrided, followed by a repeat first-stage procedure[38,39].

Depending on the size of the defect, the autologous cancellous graft can be harvested from the anterior or posterior iliac crests, proximal tibial metaphysis, or medullary canal of the femur using the Reamer-Irrigator-Aspirator (RIA) system (DePuy Synthes)[38,100,101]. For large defects, the bone graft can be augmented with bone substitutes (cancellous allograft or synthetic graft) in a ratio of less than 1 (substitutes):3 (autologous)[38,102], with the addition of osteoprogenitor

TABLE III (*continued*)

Definitive Fixation Method	Bone Graft	Mean Follow-up	Union Rate	Mean Time to Union	Complications	Secondary Procedures
NR	NR	28 mo	89.20%	13 mo	NR	Exchange nailing: 12 Revision ORIF: 28
NR	RIA: 48 ICBG: 9 AC: 25 BMP: 10	NR	DIM: 29 (93.5%) MIM: 35 (92.1%)	NR	Superficial infection: 3 Deep infection: 16 Amputation: 5	Revision grafting: 11
NR	RIA: 39 ICBG: 10 AC: 30 BMP: 1	NR	DIM: 12 (100%) MIM: 31 (92.1%)	NR	Superficial infection: 2 Deep infection: 9 Amputation: 2	Revision grafting: 15
Plate: 9 IM nail: 8	ICBG: 17	NR	15 of 17	15.1 ± 9.0 mo	Osteomyelitis: 6 Deep infection: 8	Repeat debridement and cement spacer: 1 Below-the-knee amputation: 1 Revision grafting: 5 Revision ORIF: 14
NR	ICBG: 27	21 to 60 mo	100%	280 days	None	Corrective surgery for deformity: 1
Plate: 1	NR	NR	1 of 1	330 days (240 to 360 days)	NR	NR
Plate: 14	NR	NR	14 of 14	297 days (240 to 360 days)	NR	NR
Plate: 6	NR	NR	6 of 6	260 days	NR	NR
IM nail: 1	NR	NR	1 of 1	270 days	NR	NR
External fixation: 1 IM nail: 1	NR	NR	2 of 2	335 days (310 to 360 days)	NR	NR
Plate: 2	NR	NR	2 of 2	195 days (180 to 210 days)	NR	NR
Plate: 1	NR	NR	1 of 1	180 days	NR	NR

cells from bone marrow aspirate, and/or with osteoinductive factors[38,103,104].

The defect should be filled with graft material, which should be contained within the membrane, and overstuffing of the void should be avoided. For a tension-free closure, the membrane can be mobilized to its periphery from the subcutaneous and fascia layers as required. Both the spacer and the graft should be distributed evenly across the defect, making sure that they overlap the bone ends and are contained using a continuous suture repair of the incised membrane[38].

The osteosynthesis during this second stage may also be revised (Fig. 1) or augmented (Fig. 2) as required to allow the patient to perform active functional rehabilitation.

Reported Outcomes of the Masquelet Technique for Acute Long-Bone Defects

The use of the MIMT solely for acute bone loss is infrequently reported in the literature. A recent systematic review and meta-analysis of 643 tibial defects established that the MIMT achieved union in 84% of cases regardless of the defect size[105]. Improved membrane quality was seen when the defect was covered by muscle, and therefore muscle coverage would likely be preferred to fasciocutaneous flaps[106]. Across all sites, union has been reported in 82% to 91% of cases, residual deep infection in 4% to 8%, superficial infection in 3% to 5%, and refracture in 1% to 1.5%[107]. The most common serious concerns in all reports relevant to this method are the development of a fracture-related infection and/or of a nonunion; the latter was often associated with fatigue failure of the fixation system[107].

We identified 3 case series of >20 patients that reported on this technique (Table III)[108-110]. They included a total of 164 patients (who had 66 femora with a mean bone defect of 7 cm, 95 tibiae with a mean bone defect of 6.1 cm, 2 humeri with a mean bone defect of 4 cm, and 1 ulna with a defect of 4 cm). All patients presented with an open fracture, and soft-tissue reconstruction was required in 94 cases.

The results reported in these case series are summarized below according to the location of the injury.

Tibia (Mean Bone Defect of 6.1 cm)

Diaphyseal fractures were predominantly stabilized with intramedullary nailing, whereas periarticular fractures were predominantly stabilized with plate fixation[108-110]. The mean time to the second stage ranged from 6 to 14 weeks following the first stage. In the majority of cases, RIA graft was used. The reported mean time to union ranged from 8 to 15 months. Sixteen patients underwent reoperation for delayed union (involving bone grafting in all cases and revision fixation in 14

TABLE IV Grades of Recommendations for the Use of the Masquelet Induced Membrane Technique for Acute Bone Loss

Recommendation	Grade*
The Masquelet technique is an effective method of managing acute bone defects	B
Prompt administration of broad spectrum of antibiotics	B
Prompt identification of hard signs of ischemia or, if in doubt, emergency diagnostics (CT angiography or intraoperative angiography) and restoration of blood flow (temporary shunting, graft reconstruction, or vessel repair) optimally within 3 to 4 hours are essential for the survivorship of the limb	B
Urgent primary surgical debridement of high-energy open fractures within 12 hours or even 24 hours for the lower-energy ones	B
Time to definitive soft-tissue cover within the first 7 days from the accident is associated with better clinical outcomes	B
Meticulous debridement of nonviable bone at all stages of the technique is important for a successful outcome	B
The addition of antibiotics to the cement spacer is effective for promoting the creation of a viable induced membrane	C
Intramedullary nailing appears to be mechanically superior with regard to the remodeling potential of the grafted defect and requires smaller volumes of graft at the second stage	B
The duration of the interim period is mostly dictated by the recovery of the soft tissues and the absence of signs of an infection; it usually lasts between 6 and 14 weeks	C
Evidence of an infection requires debridement of the membrane and surrounding soft tissues and reinitiation of the technique	C

*According to Wright[117], grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention; grade B, fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention; grade C, poor-quality evidence (Level-IV or V studies with consistent findings) for or against recommending intervention; and grade I, insufficient or conflicting evidence not allowing a recommendation for or against intervention.

cases). Complications in general affected 25% to 47% of the patients in the studies, including 3 superficial infections and 24 deep infections. Six patients underwent amputation. Of note, the complication rates in these 3 recent case series[108-110] compare unfavorably with the results of previous large studies of acute bone loss treated with the induced membrane or bone transport techniques[19,88,111-115].

Femur (Mean Bone Defect of 7 cm)

Steffenson et al.[110] reported on 51 femoral fractures treated using a combination of external fixation and plate fixation, and Kasha et al.[108] reported on 15 femoral fractures that were all treated using internal fixation (intramedullary nail or plate). The mean time to the second stage varied from 6 to 14 weeks, with RIA graft predominantly used. Kasha et al.[108] reported union in all 15 cases. Steffenson et al.[110] reported a 92% union rate, with union of all diaphyseal fractures compared with 79.5% of metaphyseal ones. The mean times to union were 330 and 390 days. There were 2 superficial infections and 9 deep infections. Fifteen fractures required revision grafting because union was delayed, and 2 fractures required a transfemoral amputation (Table III).

Upper Limb (Mean Bone Defect of 4 cm)

Kasha and Yalamanchili[116] reported 3 cases of use of the Masquelet technique used to treat upper-limb bone loss, including in 2 humeri and 1 ulna. All underwent fixation with plates, and the second stage occurred between 6 and 7 weeks following the index procedure. All 3 patients received an iliac crest graft and achieved complication-free union between 6 and 7 months following the second stage.

Cost Implications

Two recent publications showed the cost implications of managing acute bone loss with the MIMT[26,99]. Norris et al.[111] performed a large database analysis evaluating the hospital costs at 12 months after the index surgical procedure for segmental bone defects of different long bones treated with different methods. The mean cost was $86,453 for acute bone defects after an open fracture. Complications such as nonunion (31.3%) and fracture-related infection (23.6%) were found to result in major increases in the overall cost.

Kanakaris et al. compared the cost of the MIMT with that of bone transport in a best-case-scenario cost analysis[29]. For comparable acute bone defects (mean length, 5.08 cm), MIMT demonstrated a faster time to union with fewer reinterventions and a lower number of visits to the outpatient clinic, reducing the overall cost of treatment from £25,364 for bone transport to £17,407 for the MIMT. However, further evidence would be required before definitive conclusions with regard to efficacy and cost can be determined.

Summary

Bone loss after open fracture remains a challenging clinical entity, requiring multidisciplinary management and prolonged treatment. A summary of practice recommendations is shown in Table IV.

Ideally, patients should be managed in specialized units with around-the-clock availability of experts in soft-tissue and bone reconstruction.

The MIMT represents one of the options that can be used to restore the missing bone and has a lower cost compared with distraction osteogenesis. Meticulous planning during the different phases of reconstruction and adherence to the developed principles and tips and tricks can provide reproducible and good results. ■

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