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Open fractures: Current treatment perspective

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Summary: Severe open fractures present challenges to orthopaedic surgeons worldwide, with increased risks of significant complications. Although different global regions have different resources and systems, there continue to be many consistent approaches to open fracture care. Management of these complex injures continues to evolve in areas ranging from timing of initial operative debridement to the management of critical-sized bone defects. This review, compiled by representative members of the International Orthopaedic Trauma Association, focuses on several critical areas of open fracture management, including antibiotic administration, timing of debridement, bone loss, soft tissue management, and areas of need for future investigation.

Key Words: open fractures, antibiotic administration, surgical timing, bone defect, wound coverage

1. Introduction

The treatment of severe open fractures remains challenging for orthopaedic surgeons in trauma care. Compared with closed fractures, open fractures are considered to have a higher risk of infection, nonunion, incidence of bone loss, and soft tissue–related complications. Accordingly, a multidisciplinary approach, which includes orthopaedic and plastic surgical teams, often benefits patients with severe open fractures. The most debated controversies in the management of open fractures include administration of antibiotics, timing of initial operative debridement, management of critical-sized bone defects, and time to wound coverage. The purpose of this review was to present information on current treatments of these issues as compiled by representative members of the International Orthopaedic Trauma Association.

2. Antibiotic Administration: Local Treatment Methods

2.1. Continuous Local Antibiotic Perfusion

To decrease the risk of infection after severe open fractures, early administration of intravenous antimicrobials and soft tissue management including appropriate debridement is critical. Postoperative bone and soft tissue infections are often intractable because of the formation of bacterial biofilms and the inability of antimicrobial agents to reach the bacteria. To break down the biofilm and quell the infection, antimicrobial concentrations should reach the minimum biofilm eradication concentration, which is 100–1000 times the minimum inhibitory concentration. However, achieving minimum biofilm eradication concentration is not possible through intravenous administration. Although antibiotic-loaded bone cements and beads have been suggested as carriers, these materials will not provide for the maintenance of high local antimicrobial concentrations over an extended period of time as the antibiotics eluted from these carriers decrease to minimum inhibitory concentration levels within a few days of administration.[1] One novel method, continuous local antibiotic perfusion (CLAP), can indeed maintain a constant, therapeutic local antibiotic concentration for a longer period of time with less invasiveness and fewer complications than other methods.

2.2. iMAP and iSAP

CLAP is different from traditional locally applied methods because the continuously infused antibiotic solution is applied directly adjacent to the contaminated area and directed there through negative pressure. CLAP includes methods such as intra–soft tissue antibiotic perfusion (iSAP) and intramedullary antibiotic perfusion (iMAP). They can be applied separately or in combination, depending on the contaminated focus.[2]

iMAP, used to decrease the risk of bone infections, is applied through a bone marrow needle that is inserted adjacent to the contaminated area of the bone. When possible, 2 needles are placed so that the affected area is between the infusion sources.

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First, a hole is made in the cortical bone with a 2.4-mm Kirschner wire, and a bone marrow needle is inserted using a mallet. Contrast media should be injected to ensure that the antibiotic reaches the planned location.

iSAP is specifically used to decrease the risk of soft tissue infections and manage dead spaces. To maximize the area treated, the tip of the dual-lumen tube from which the antimicrobial is released should be placed deep into the dead space void. Then, the discharge holes of the dual-lumen tube should be placed over a wide area of the space. As a result, the contaminated area is saturated with antibacterial drugs, and negative pressure is applied uniformly and drained sufficiently to prevent dead space formation.

After application, for 14 days after surgery, gentamicin (60 mg/50 cc) is continuously administered at a low flow rate (2 mL/h) by a syringe pump through the bone marrow puncture needles and dual-lumen tubes. Gentamicin blood concentration greater than 2 μg/mL may cause side effects (renal dysfunction and hearing impairment), and monitoring of blood concentration is required. Systemic administration of antibiotics based on drug sensitivity also is necessary. In the Steel Memorial Hirohata Hospital in Japan, treatment with the CLAP procedure was approved by the Certified Clinical Research Review Board as an off-label use for aminoglycoside antibiotic administration.

Investigators reported treating fracture-related infections with CLAP by iMAP early after osteosynthesis in 10 cases, successfully treating infections while preserving implants in all patients.[3] In addition, Ohno et al reported iSAP and iMAP use in combination to treat 3 cases of severe open fractures with soil contamination, noting uncomplicated healing. To determine how the fluid used in iMAP therapy is distributed and how the iSAP system is affected by negative pressure wound therapy, Maruo et al conducted basic research with lower legs of cadaver models. Axial and sagittal sections of specimens with and without iSAP revealed that the injected dye was guided to the fracture site by using iSAP, unlike traditional administration where the dye remained in the venous system.[4]

2.3. Future Directions

In summary, CLAP was introduced as a novel approach for local antibiotic administration, having the benefits of maintaining higher levels of antibiotics locally over an extended period of time. iMAP is most beneficial when applied in combination with iSAP. With these techniques, blood concentrations of gentamicin must be monitored, with maintained levels less than 2 μg/mL to prevent systemic side effect of gentamicin. CLAP may provide an option to directly control local infections with less systemic complications in future practice.

3. Surgical Timing: Which Fractures, What Time?

The optimal timing in which to perform the initial debridement of open tibial fractures still remains controversial.

3.1. History of "Six-Hour Rule"

Traditionally, open fractures have been considered emergencies, with initial surgical debridement recommended within the first hours after injury, a term called the "6-hour rule." This historic recommendation was based on a study conducted by Friedrich in 1898, where he was able to show that the rate of bacterial replication increased exponentially after 6 hours in soft tissue lesions in guinea pigs.[5] Only 2 articles in the literature support Friedrich's initial observations. Kreder and Armstrong[6] reported in a retrospective study of 56 pediatric patients that the infection rate in fractures debrided within 6 hours was 12%, compared with a rate of 25% for those operated after 6 hours. Kindfater and Jonassen[7] also reported increased complications and infections when debridement was performed after the first 5 hours (38%) relative to those within 5 hours (7%). However, in this study, the groups were not homogeneous, and the most of serious fractures were in the group where time to initial debridement exceeded 5 hours from injury.

3.2. Evidence Against the "Six-Hour Rule"

One of the first studies demonstrating that there was no relationship between surgical timing and infection rate was that of Patzakis and Wilkins in 1989.[8] They analyzed 1100 patients with open fractures and found infection rates of 6.8% and 7.1%, respectively, for fractures operated on before and after 12 hours. They showed that the most important factor in reducing the infection was the time to antibiotic administration. In 2007, in a systematic review, Crowley and Gianoudis[9] found no relationship between surgical timing and infection rate, establishing that the arbitrary time of 6 hours should be re-evaluated. In 2010, Pollack and LEAP group investigators[10] published a multicenter study on 315 patients. They reported that while the time to initial debridement was not an independent predictive factor of infection, the time from injury to the referral of the patient to the Level I hospital was. They suggested that this finding could be related to a more rapid administration of the antibiotics and resuscitation of the polytrauma patient. In 2014, Hull et al[11] showed that each additional hour of delay of the initial debridement increased the risk of infection but only demonstrated this in severe IIIB Gustilo open tibial fractures. Prodromis et al,[12] in 2016, performed a meta-analysis and a systematic review to evaluate infection and nonunion rates in open tibial fractures treated with initial debridement before and after 6 hours. They showed no significant differences between the groups with respect to infection rates and nonunion rates. In 2018, Hendrickson et al[13] performed a retrospective study on the incidence of deep infection in GA type IIIB open tibial fractures debrided before and after 12 hours. There was no statistically significant difference reported between the groups (4.8% vs. 5.2%, respectively). There was statistically no difference between both groups.

3.3. General Recommendations

Although there is largely consensus that time to initial debridement is not the most critical factor in rates of posttraumatic complications for open fractures, there is still a lack of agreement on what is the ideal time to perform the initial debridement. General recommendations include (1) antibiotic coverage should be performed as quickly as possible, preferably within 1 hour after fracture; (2) the indications for immediate surgery in the emergency includes gross contamination of the wound (eg, when debris is clearly visible or involves agricultural, marine, or sewage contamination), severe polytrauma, open fractures with associated irreducible joints, and acute compartment or vascular syndrome; and (3) as possible, primary debridement should be performed by an experienced team that includes orthopaedic and plastic surgeons and scheduled during normal working hours with full equipment and supplies available within the first 12–24 hours.

4. Critical-Sized Bone Defect: Current Evidence

4.1. Definition and Therapeutic Approaches

The management of critical-sized bone defects represents a major clinical orthopaedic challenge in high-grade open fractures.[13,14]

Critical-sized bone defects are defined as those that will not heal spontaneously during the patient's lifetime, with a defect size length greater than 1–2 cm and greater than 50% loss of the circumference of the bone.[14,16,17] There are a variety of therapeutic approaches to these challenging problems, including bone grafting, distraction osteogenesis, the Masquelet technique, and tissue engineering approaches.

4.2. Bone Grafting

Cancellous autologous bone graft remains the gold standard for the treatment of bone loss, providing osteoconductive, osteoinductive, and osteogenic factors. Moreover, it is nonimmunogenic and does not carry the risk of transmissible infections.[18] Autograft can be harvested from the anterior and/or posterior iliac crests, with a complication rate of approximately 20%, with pain at the harvested site reported in 18% of the patients. However, for large segmental defects, the morbidity associated with the harvest required to fill the defect is substantial; in addition, the amount of the graft is finite.[19] More recently, the Reamer/Irrigator/Aspirator device (DePuy Synthes, West Chester, PA) has offered a new method for obtaining bone graft, reducing the reaming related problems of thermal necrosis and marrow content embolism through simultaneous irrigation of the canal and aspiration of reaming debris.[20] In addition, the volume of bone graft obtained with Reamer/Irrigator/Aspirator is larger than that obtained from anterior iliac crest harvesting, with a lower rate of complications, averaging around 6%.[19] Currently, cancellous autograft is recommended for defects less than 5 cm, with well-vascularized, healthy recipient sites that do not require structural integrity of the graft.[21] Cancellous heterologous bone graft has several benefits, including availability of graft, avoidance of donor site morbidity, and the ability of the graft to provide structural support with a relatively easier surgical technique. However, cancellous autograft is not vascularized and has a limited ability to integrate with the host bone. Moreover, no osteogenic potential, increased risk of disease transmission, and immunogenic response are associated with this procedure.[22,23] In general, cadaveric allograft is used mostly for massive oncologic-related defects and is not commonly used for defects arising in the setting of trauma.

4.3. Distraction Osteogenesis

Distraction osteogenesis, introduced in the 1950s by Ilizarov,[24] uses the bone's natural capacity for regeneration under tension. With this technique, the process of bone formation in the distraction gap is histologically similar to intramembranous ossification.[25] The method uses a corticotomy made in healthy metaphyseal bone to create a free segment of living bone followed by distraction toward the defect site, with bone production occurring de novo between the 2 corticotomy surfaces.[24] Distraction–compression transport is achieved mechanically by attaching the segmental fragments to a circular external fixator with tensioned wires that allows for distraction at the corticotomy site and compression at the docking site.[26] The Ilizarov technique has been reported to have good results in all long bones in the body, with an overall union rate of 95%.[27] This technique can also be used to correct alignments in any plane, including rotational deformities, because it uses a circumferential ring fixator. Despite the fact that this technique is well established, some disadvantages exist, including prolonged treatment time, pin site infection, pin breakage, soft tissue pain around the external fixator, nerve stretching, and joint contractures.[28]

4.4. Masquelet Technique

A recent technique, introduced by Masquelet, which he termed "induced membrane," is a two-stage procedure that uses a temporary cement spacer initially, stabilized by plate or nail, followed by subsequent bone grafting.[29] During the first 6–8 weeks, the polymethacrylate cement spacer (with eventual addition of antibiotics) induces a fibrous membrane all around the gap, preventing hematoma formation and fibrous tissue ingrowth into the bone defect. Interestingly, the fibrous membrane is highly vascularized and contains various osteoinductive factors.[30,31] After this period, the membrane is incised, the spacer is removed, and autograft is packed into the pseudocapsule.[32] The results of this technique are favorable, with a union rate of 88%–100% in trauma cases.[33,34] Reported complications of the induced membrane technique include infection, which is the most common, amputation, malunion, fracture, and nonunion.[29–35]

4.5. Tissue Engineering

The most recent advances in the area of bone loss management have been devoted to tissue engineering strategies, which involve osteoconductive scaffolds, osteoinductive growth factors, and cells with osteogenic potentials. Ceramics, such as bioactive glass and tricalcium phosphate, are a commonly used for bone scaffolds. Hydroxyapatite and synthetic biodegradable polymers have been used to coat materials, in an attempt to improve their mechanical and osteogenic potential.[36–38] Collagen, alginate, and hyaluronic acid are considered natural substitutes used for scaffolds, with excellent abilities to release of osteoinductive factors, but have poor intrinsic material mechanical properties.[39,40] Future research will continue to focus on improving the osteogenic properties of polymer–ceramic scaffolds, including techniques to add bone marrow mesenchymal stem cells, incorporate growth factors, and timed release of factors throughout the healing process.[41–43]

5. Wound Coverage: Vacs to Flaps

5.1. Orthoplastic Approach

It is increasingly recognized that the treatment of severe open long bone injuries using combined orthopaedic and plastic surgical expertise can substantially improve outcomes.[44–47] Most of these injuries require a multistage approach, with negative pressure dressings being a modality of choice as an interim measure until definitive coverage can be achieved.[48–51] Many articles look at the time from injury to definitive coverage, which has been correlated with infective risk, but what has been less clear is how long interim dressings, predominantly negative pressure methods, can safely applied.[52–54]

5.2. Recent Direction of the Decision-Making Process

What surgeon would champion undertaking a knee arthroplasty, covering the wound with a wound vac and a referral to plastics for closure? Clearly, a ridiculous suggestion, but one that mirrors the situation with open tibial fractures, the most common open long bone fracture. In many centers worldwide, the debridement and definitive fixations are undertaken by orthopaedic surgeons, the wound is covered with a negative pressure dressing, and the case is referred to a plastic surgeon for soft tissue coverage. The delay in this process is reported to take up to 6 weeks, even in modern series.[52] Unlike the controlled arthroplasty scenario, the massive energy transfer to the injured

limb means an extensive zone of tissue injury and, therefore, a much more precarious environment.

6. Problems With Conventional Approach

The FLOW investigators[55,56] found the use of wound vac dressings to be associated with a higher rate of deep infection requiring operative management and a subsequent lower quality of life at 6 months. Similarly, a study of 14 North American trauma centers established that the time between definitive fixation and cover is critical; the more prolonged, the higher the rates of deep infection.[52] Pincus et al[54] quantified this as a 40% increase for each week delay overall. The reported rates range from the high teens to over 30%, figures that would be unacceptable in any other part of orthopaedic practice.

6.1. National Guidelines in the United Kingdom

In the UK system, national guidelines[57,58] and system reconfiguration have driven practice in the treatment of open tibial fractures toward combined debridement by experienced orthopaedic and plastic surgeons, followed by definitive fixation and coverage in the same surgical episode within 72 hours. This has greatly reduced variation with deep infection figures for open tibia fractures nationally being consistently at 7%.[51,59]

Overall, wound vac dressings retain a role in most practices but are not equivalent to coverage, and each system needs to attempt to reduce the window between definitive fixation and soft tissue coverage to make meaningful improvements in care.

6.2. Open Fractures: What Are the Top Research Questions?

Surgical site infection (SSI), in the context of open fractures, is a devastating complication which can lead to nonunion, wound complications, reoperation, and amputation. Infection prevention represents a crucial research area that has significant implications in optimizing patient outcomes and reducing the economic cost of these injuries.[60] Prompt prophylactic systemic antibiotic administration with adequate surgical irrigation and timely debridement remain the pillars of SSI prevention in open fractures.[53,61,62] Intraoperatively, the effects of delivery of irrigation, local antibiotics, and antibiotic-coated implants have been examined as considerations in the prevention of SSI. The Fluid Lavage of Open Wounds Trial demonstrated that low pressure irrigation is an acceptable low-cost alternative for surgical irrigation.[63] Local antibiotic administration represents a possible tool to overcome impaired local vascularity that can be seen in high-energy open fractures.[64] The VANCO randomized trial showed significantly lower rates of deep gram-positive SSI after local vancomycin powder administration, 3.7% versus 7.8%, when compared with the control group.[65] The TOBRA trial is an ongoing prospective randomized controlled trial that will provide valuable information regarding the efficacy of topical gram-negative coverage in open fractures.[66] Antibiotic-coated hardware represents another possible strategy to prevent implant-related SSI. Retrospective evidence from Greco et al[67] comparing gentamicin-coated and uncoated intramedullary nails in acute management of 42 open diaphyseal tibia fractures demonstrated no difference in radiographic healing or overall infection rates. A possible advantage was seen in high-grade injuries as 3 of 5 patients treated with uncoated nails versus 2 of 11 patients with coated nails developed infection.[67] Similarly, Franz et al[68] noted a 75% infection reduction in high-grade open tibia fractures with an associated cost savings of 15%. Other methods of antimicrobial coatings such as silver and povidone–iodine remain relatively novel and have not been tested in the setting of open fractures.[69–71] Overall, there is a substantial lack of evidence evaluating these strategies to deliver local antimicrobial coverage. Future research evaluating local antimicrobial therapies in open fractures should be directed toward addressing questions regarding cost effectiveness, safety, potential for local and systemic toxicity, and efficacy of these strategies with a particular focus on their potential in the settings of polymicrobial infections and compromised host immunity.

Nonunion in the setting of an open fracture is a devastating complication with significant impacts on patient quality of life and level of functioning.[72] The ability to identify at-risk patients early in their postoperative course would allow clinicians to alter management when appropriate to optimize patient outcomes. As a result, developing methods to reliably and accurately predict fracture healing in open fractures has drawn significant research interest. The Radiographic Union Score for Tibial Fractures and the modified Radiographic Union Score for Tibial Fractures are reliable objective tools that score radiographic features of fracture healing in diaphyseal tibial fractures.[73–75] Meanwhile, the Nonunion Risk Determination Score is a predictive scoring system that tallies various patient, injury, and clinical considerations to estimate the risk of progression to nonunion at the time of fracture fixation.[76,77] While these tools are promising, more accurate imaging modalities, such as microdose CT, are needed to further validate these scoring systems and define critical scoring thresholds that would trigger further investigation and intervention.[78] As well, there is emerging interest in identifying screening serum biomarker panels including bone turnover markers, growth factors, cytokines, proteins, immune cells, and mRNAs that can provide early evidence of impaired healing in high-risk patients.[79] The ideal biomarkers should be highly sensitive and specific for the detection of nonunion in the face of an open fracture, while easily measured and inexpensive.[79] Further evidence is needed to define their role in the early identification of nonunion in the setting of an open fracture.

With advances in nonunion identification and risk stratification, augmentation of fracture repair has become a priority. Autograft remains the gold standard for augmentation of fracture healing and management of bone defects. Given that autograft harvesting is not a benign procedure, with reported rates of donor site morbidity as high as 18%–48%, the suitability of other therapies including various osteobiologic substances such as Bone Morphogenic Proteins and Bone Marrow Aspiration Concentration have been examined.[19,80,81] Conflicting evidence regarding the use of BMPs has been reported in the context of open tibia fractures with little evidence showing an advantage beyond reamed IM nail fixation alone.[82,83] At present, there is minimal role for BMPs in open fractures given the inadequate evidence supporting positive treatment effects coupled with known side effects such as osteolysis and heterotopic ossification.[84] Bone Marrow Aspiration Concentration presents a minimally invasive alternative to autograft with high concentrations of mesenchymal stem cells and growth factors presenting theoretical benefits in achieving and potentially accelerating bone union.[85] Moving forward, level I evidence in needed to standardize graft harvest, method of centrifugation, cell count concentration, and administration as there is significant heterogeneity within current practices.[64] Finally, the overall timing and approach to definitive management of bone defects remain controversial. The Masquelet technique is often used as initial management of acute bone defects with promising rates of boney union.[86] However, there is

significant variability within the best available evidence for timing and technical aspects of the procedure.[87] Further research is needed to understand predictors of optimal timing of the second stage, graft choices, healing adjuncts, autograft alternatives, critical thresholds of bone defects, and patient factors that influence operative outcomes.

7. Conclusion

Although there is general agreement worldwide on many of the critical principles of open fracture management, there are still areas of controversy. The timing, type, and method (ie, local vs. systemic) continue to develop. The traditional "6-hour rule" has been challenged, with the ideal time to perform the initial debridement still under debate; debridements are believed to benefit from an experienced team that includes orthopaedic and plastic surgeons during normal working hours where full equipment and supplies are available within the first 12–24 hours. Wound vac dressings retain a role in most practices but are not equivalent to coverage, and each system should attempt to reduce the window between definitive fixation and soft tissue coverage to improve outcomes. The management of open fracture care will continue to evolve with continued investigation, including questions aimed at understanding the optimal administration of antibiotics, timing of initial and subsequent debridements, healing adjuncts and autograft alternatives, thresholds for managing of bone defects, and enhancement of patient factors that influence postinjury outcomes.

References

1. Anagnostakos K, Kelm J. Enhancement of antibiotic elution from acrylic bone cement. *J Biomed Mater*. 2009;90:467–475.
2. Himeno D, Matsuura Y, Maruo A, et al. A novel treatment strategy using continuous local antibiotic perfusion: a case series of a refractory infection caused by hypervirulent *Klebsiella pneumoniae*. *J Orthop Sci*. 2022;27:272–280.
3. Maruo A, Oda T, Miya H, et al. Intra-medullary antibiotics perfusion (iMAP) for the control of fracture-related infection early after osteosynthesis. *J Orthop Surg* (Hong Kong). 2021;29:1–10.
4. Maruo A, Fukui T, Oe K, et al. Intra-medullary distribution of antibiotics by intra-medullary antibiotics perfusion (iMap)-A cadaver study. *Kossetsu Jpn*. 2020;42:1–5.
5. Friedrich PL. Die aseptische Versorgung frischer Wunden, unter Mittheilung von Thier- Versuchen über die Auskeimungszeit von Infectionserregern in frischen Wunden. *Scientific pamphlet* 1896.
6. Kreder HJ, Armstromg P. A review of open tibial fractures in children. *J Pediatr Orthop*. 1995;15:482–488.
7. Kindsfater K, Jonassen EA. Osteomyelitis in grade II and III open tibia fractures with late debridement. *J Orthop Trauma*. 1995;9:121–127.
8. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. *Clin Orthop Relat Res*. 1989;243:36–40.
9. Crowley DJ, Kanakaris NK, Giannoudis PV. Debridement and wound closure of open fractures: the impact of the time factor on infection rates. *Injury*. 2007;38:879–889.
10. Pollak AN, Jones AL, Castillo RC, et al. The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. *J Bone Joint Surg Am*. 2010;92-A:7–15.
11. Hull PD, Johnson SC, Stephen DJ, et al. Delayed debridement of severe open fractures is associated with a higher rate of deep infection. *Bone Joint J*. 2014;96-B:379–384.
12. Prodromidis AD, Charalambous CP. The 6-hour rule for surgical debridement of open tibial fractures: a systematic review and meta-analysis of infection and nonunion rates. *J Orthop Trauma*. 2016;30:397–402.
13. Hendrickson SA, Wall RA, Manley O, et al. Time to initial debridement and wound excision (TIDE) in severe open tibial fractures and related clinical outcome: a multi-centre study. *Injury*. 2018;49:1922–1926.
14. Nauth A, McKee MD, Einhorn TA, et al. Managing bone defects. *J Orthop Trauma*. 2011;25:462–466.
15. Toogood P, Miclau T. Critical-sized bone defects: sequence and planning. *J Orthop Trauma*. 2017;31:S23–S26.
16. Roddy E, DeBaun MR, Daoud-Gray A, et al. Treatment of critical-sized bone defects: clinical and tissue engineering perspectives. *Eur J Orthop Surg Traumatol*. 2018;28:351–362.
17. Keating JF, Simpson AHRW, Robinson CM. The management of fractures with bone loss. *J Bone Joint Surg Br*. 2005;87-B:142–150.
18. Bauer TW, Muschler GF. Bone graft materials. An overview of the basic science. *Clin Orthop Relat Res*. 2000;(371):10–27.
19. Dimitriou R, Mataliotakis GI, Angoules AG, et al. Complications following autologous bone graft harvesting from the iliac crest and using the RIA: a systematic review. *Injury*. 2011;42:S3–S15.
20. van de Wall BJM, Beeres FJP, Rompen IF, et al. RIA versus iliac crest bone graft harvesting: a meta-analysis and systematic review. *Injury*. 2021;53: 286–293.
21. Goulet JA, Senunas LE, DeSilva GL, et al. Autogenous iliac crest bone graft: complications and functional assessment: *Clin Orthop Rel Res*. 1997;339:76–81.
22. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury*. 2005;36:S20–S27.
23. Ng VY. Risk of disease transmission with bone allograft. *Orthopedics*. 2012;35:679–681.
24. Ilizarov GA. The principles of the Ilizarov method. *Bull Hosp Joint Dis Orthop Inst*. 1988;48:1–11.
25. Sailhan F Bone lengthening (distraction osteogenesis): a literature review. *Osteoporos Int*. 2011;22:2011–2015.
26. Aktuglu K, Erol K, Vahabi A. Ilizarov bone transport and treatment of critical-sized tibial bone defects: a narrative review. *J Orthop Traumatol*. 2019;20:22.
27. Papakostidis C, Bhandari M, Giannoudis PV. Distraction osteogenesis in the treatment of long bone defects of the lower limbs: effectiveness, complications and clinical results; a systematic review and meta-analysis. *Bone Joint J*. 2013;95-B:1673–1680.
28. Paley D. Problems, obstacles, and complications of limb lengthening by the Ilizarov technique. *Clin Orthop Relat Res*. 1990;250:81–104.
29. Masquelet AC, Begue T. The concept of induced membrane for reconstruction of long bone defects. *Orthop Clin North Am*. 2010;41:27–37.
30. Aho O-M, Lehenkari P, Ristiniemi J, et al. The mechanism of action of induced membranes in bone repair. *J Bone Joint Surg*. 2013;95:597–604.
31. Cuthbert RJ, Churchman SM, Tan HB, et al. Induced periosteum a complex cellular scaffold for the treatment of large bone defects. *Bone*. 2013;57:484–492.
32. Giannoudis PV, Faour O, Goff T, et al. Masquelet technique for the treatment of bone defects: tips-tricks and future directions. *Injury*. 2011; 42:591–598.
33. Apard T, Bigorre N, Cronier P, et al. Two-stage reconstruction of post-traumatic segmental tibia bone loss with nailing. *Orthop Traumatol Surg Res*. 2010;96:549–553.
34. Gouron R, Deroussen F, Plancq M-C, et al. Bone defect reconstruction in children using the induced membrane technique: a series of 14 cases. *Orthop Traumatol Surg Res*. 2013;99:837–843.
35. Karger C, Kishi T, Schneider L, et al. Treatment of posttraumatic bone defects by the induced membrane technique. *Orthop Traumatol Surg Res*. 2012;98:97–102.
36. Rezwan K, Chen QZ, Blaker JJ, et al. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. *Biomaterials*. 2006;27:3413–3431.
37. Ardeshirylajimi A, Farhadian S, Jamshidi Adegani F, et al. Enhanced osteoconductivity of polyethersulphone nanofibres loaded with bioactive glass nanoparticles in *in vitro* and *in vivo* models. *Cell Prolif*. 2015;48: 455–464.
38. Ardeshirylajimi A, Hosseinkhani S, Parivar K, et al. Nanofiber-based polyethersulfone scaffold and efficient differentiation of human induced pluripotent stem cells into osteoblastic lineage. *Mol Biol Rep*. 2013;40: 4287–4294.
39. Jin H-H, Kim D-H, Kim T-W, et al. In vivo evaluation of porous hydroxyapatite/chitosan–alginate composite scaffolds for bone tissue engineering. *Int J Biol Macromol*. 2012;51:1079–1085.
40. Li Z, Ramay HR, Hauch KD, et al. Chitosan–alginate hybrid scaffolds for bone tissue engineering. *Biomaterials*. 2005;26:3919–3928.
41. Liu Y, Ming L, Luo H, et al. Integration of a calcined bovine bone and BMSC-sheet 3D scaffold and the promotion of bone regeneration in large defects. *Biomaterials*. 2013;34:9998–10006.
42. Jun S-H, Lee E-J, Jang T-S, et al. Bone morphogenic protein-2 (BMP-2) loaded hybrid coating on porous hydroxyapatite scaffolds for bone tissue engineering. *J Mater Sci Mater Med*. 2013;24:773–782.

43. Kang Y, Scully A, Young DA, et al. Enhanced mechanical performance and biological evaluation of a PLGA coated β-TCP composite scaffold for load-bearing applications. *Eur Polym J*. 2011;47:1569–1577.
44. Nayagam S, Graham K, Pearse M, et al. Reconstructive surgery in limbs: the case for the orthoplastic approach. *Ann Plast Surg*. 2011;66:6–8.
45. Glass GE, Pearse MF, Nanchahal J. Improving lower limb salvage following fractures with vascular injury: a systematic review and new management algorithm. *J Plast Reconstr Aesthet Surg*. 2009;62:571–579.
46. Naique SB, Pearse M, Nanchahal J. Management of severe open tibial fractures: the need for combined orthopaedic and plastic surgical treatment in specialist centres. *J Bone Joint Surg Br*. 2006;88-B:351–357.
47. Khan U, Kelly MB, Pleat J, et al. Orthoplastics: an integral evolution within comprehensive trauma care. *Injury*. 2011;42:969–971.
48. Fowler T, Whitehouse M, Riddick A, et al. A retrospective comparative cohort study comparing temporary internal fixation to external fixation at the first stage debridement in the treatment of type IIIB open diaphyseal tibial fractures. *J Orthop Trauma*. 2019;33:125–130.
49. Al-Hourani K, Stoddart M, Khan U, et al. Orthoplastic reconstruction of type IIIB open tibial fractures retaining debrided devitalized cortical segments: the Bristol experience 2014 to 2018. *Bone Joint J*. 2019;101-b:1002–1008.
50. Al-Hourani K, Fowler T, Whitehouse MR, et al. Two-stage combined ortho-plastic management of type IIIB open diaphyseal tibial fractures requiring flap coverage: is the timing of debridement and coverage associated with outcomes? *J Orthop Trauma*. 2019;33:591–597.
51. Costa ML, Achten J, Bruce J, et al. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: the WOLLF randomized clinical trial. *JAMA*. 2018;319:2280–2288.
52. Kuripla C, Tornetta P, III, Foote CJ, et al. Timing of flap coverage with respect to definitive fixation in open tibia fractures. *J Orthop Trauma*. 2021;35:430–436.
53. Foote CJ, Tornetta P, III, Reito A, et al. A reevaluation of the risk of infection based on time to debridement in open fractures: results of the GOLIATH meta-analysis of observational studies and limited trial data. *J Bone Joint Surg Am*. 2021;103:265–273.
54. Pincus D, Byrne JP, Nathens AB, et al. Delay in flap coverage past 7 days increases complications for open tibia fractures: a cohort study of 140 North American trauma centers. *J Orthop Trauma*. 2019;33:161–168.
55. Prada C, Marcano-Fernández FA, Schemitsch EH, et al. Timing and management of surgical site infections in patients with open fracture wounds: a fluid lavage of open wounds cohort secondary analysis. *J Orthop Trauma*. 2021;35:128–135.
56. Johal H, Axelrod D, Sprague S, et al. The effect of time to irrigation and debridement on the rate of reoperation in open fractures: a propensity score-based analysis of the Fluid Lavage of Open Wounds (FLOW) study. *Bone Joint J*. 2021;103-b:1055–1062.
57. NICE. Fractures (complex): assessment and management. 2016. Available from: https://www.nice.org.uk/guidance/ng37.
58. British Orthopaedic Association. *BOAST-open Fractures*. 2017. Available form: https://www.boa.ac.uk/resources/boast-4-pdf.html.
59. Mathews JA, Ward J, Chapman TW, et al. Single-stage orthoplastic reconstruction of Gustilo-Anderson Grade III open tibial fractures greatly reduces infection rates. *Injury*. 2015;46:2263–2266.
60. Anglen JO. Wound irrigation in musculoskeletal injury. *J Am Acad Orthop Surg*. 2001;9:219–226.
61. Lack WD, Karunakar MA, Angerame MR, et al. Type III open tibia fractures: immediate antibiotic prophylaxis minimizes infection. *J Orthop Trauma*. 2015;29:1–6.
62. Roddy E, Patterson JT, Kandemir U. Delay of antibiotic administration greater than 2 hours predicts surgical site infection in open fractures. *Injury*. 2020;51:1999–2003.
63. Investigators F A trial of wound irrigation in the initial management of open fracture wounds. *New Engl J Med*. 2015;373:2629–2641.
64. Obremskey WT, Rickert MM, Miller AN, et al. Augmentation of fracture repair: is anything ready for prime time? *Instr Course Lect*. 2022;71:329–344.
65. O'Toole RV, Joshi M, Carlini AR, et al. Local antibiotic therapy to reduce infection after operative treatment of fractures at high risk of infection: a multicenter, randomized, controlled trial (VANCO study). *J Orthop Trauma*. 2017;31:S18–S24.
66. O'Toole RV. *Novel Topical Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: TOBRA-A Multicenter RCT*. Baltimore, MD: University of Maryland school of Medicine;2020. https://apps.dtic.mil/sti/citations/AD1160547. Accessed April 21, 2023.
67. Greco T, Cianni L, Polichetti C, et al. Uncoated vs. antibiotic-coated tibia nail in open diaphyseal tibial fracture (42 according to AO Classification): a single center experience. *Biomed Res Int*. 2021;2021:7421582.
68. Franz D, Raschke M, Giannoudis P, et al. Use of antibiotic coated intramedullary nails in open tibia fractures: a European medical resource use and cost-effectiveness analysis. *Injury*. 2021;52:1951–1958.
69. Rupp M, Popp D, Alt V. Prevention of infection in open fractures: where are the pendulums now? *Injury*. 2020;51:S57–S63.
70. Tsuchiya H, Shirai T, Nishida H,et al. Innovative antimicrobial coating of titanium implants with iodine. *J Orthop Sci*. 2012;17:595–604.
71. Hardes J, Von Eiff C, Streitbuerger A, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. *J Surg Oncol*. 2010;101:389–395.
72. Brinker MR, Trivedi A, O'Connor DP. Debilitating effects of femoral nonunion on health-related quality of life. *J Orthop Trauma*. 2017;31:e37–e42.
73. Leow J, Clement N, Tawonsawatruk T, et al. The radiographic union scale in tibial (RUST) fractures: reliability of the outcome measure at an independent centre. *Bone Joint Res*. 2016;5:116–121.
74. Whelan DB, Bhandari M, Stephen D, et al. Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation. *J Trauma Acute Care Surg*. 2010;68:629–632.
75. Litrenta J, Tornetta P III, Mehta S, et al. Determination of radiographic healing: an assessment of consistency using RUST and modified RUST in metadiaphyseal fractures. *J Orthop Trauma*. 2015;29:516–520.
76. O'Halloran K, Coale M, Costales T, et al. Will my tibial fracture heal? Predicting nonunion at the time of definitive fixation based on commonly available variables. *Clin Orthop Rel Res*. 2016;474:1385–1395.
77. O'Toole RV, Jolissaint J, O'Halloran K, et al. Nurd 2.0: prediction of tibial nonunion after intramedullary nail fixation at any time within 3 months after injury. *Injury*. 2021;52:1577–1582.
78. Schwarzenberg P, Maher MM, Harty JA, et al. Virtual structural analysis of tibial fracture healing from low-dose clinical CT scans. *J Biomech*. 2019;83:49–56.
79. Chitwood JR, Chakraborty N, Hammamieh R, et al. Predicting fracture healing with blood biomarkers: the potential to assess patient risk of fracture nonunion. *Biomarkers*. 2021;26:703–717.
80. Baldwin P, Li DJ, Auston DA, et al. Autograft, allograft, and bone graft substitutes: clinical evidence and indications for use in the setting of orthopaedic trauma surgery. *J Orthop Trauma*. 2019;33:203–213.
81. Niedhart C, Pingsmann A, Jürgens C, et al. Complications after harvesting of autologous bone from the ventral and dorsal iliac crest-a prospective, controlled study. *Z fur Orthopadie ihre Grenzgeb*. 2003;141:481–486.
82. Aro HT, Govender S, Patel AD, et al. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. *J Bone Joint Surg Am*. 2011;93:801–808.
83. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am*. 2002;84:2123–2134.
84. Dumic-Cule I, Peric M, Kucko L, et al. Bone morphogenetic proteins in fracture repair. *Int Orthop*. 2018;42:2619–2626.
85. Hernigou P, Housset V, Dubory A, et al. Early injection of autologous bone marrow concentrates decreases infection risk and improves healing of acute severe open tibial fractures. *Injury*. 2022;53:S26–S33.
86. Fung B, Hoit G, Schemitsch E, et al. The induced membrane technique for the management of long bone defects: a systematic review of patient outcomes and predictive variables. *Bone Joint J*. 2020;102:1723–1734.
87. Masquelet A, Kanakaris NK, Obert L, et al. Bone repair using the Masquelet technique. *J Bone Joint Surg Am*. 2019;101:1024–1036.