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Nonunion – consensus from the 4th annual meeting of the Danish Orthopaedic Trauma Society

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- Nonunions are a relevant economic burden affecting about 1.9% of all fractures. Rather than specifying a certain time frame, a nonunion is better defined as a fracture that will not heal without further intervention.
- Successful fracture healing depends on local biology, biomechanics and a variety of systemic factors. All components can principally be decisive and determine the classification of atrophic, oligotrophic or hypertrophic nonunions. Treatment prioritizes mechanics before biology.
- The degree of motion between fracture parts is the key for healing and is described by strain theory. If the change of length at a given load is > 10%, fibrous tissue and not bone is formed. Therefore, simple fractures require absolute and complex fractures relative stability.
- The main characteristics of a nonunion are pain while weight bearing, and persistent fracture lines on X-ray.
- Treatment concepts such as ‘mechanobiology’ or the ‘diamond concept’ determine the applied osteosynthesis considering soft tissue, local biology and stability. Fine wire circular external fixation is considered the only form of true biologic fixation due to its ability to eliminate parasitic motions while maintaining load-dependent axial stiffness. Nailing provides intramedullary stability and biology via reaming. Plates are successful when complex fractures turn into simple nonunions demanding absolute stability. Despite available alternatives, autograft is the gold standard for providing osteoinductive and osteoconductive stimuli.
- The infected nonunion remains a challenge. Bacteria, especially staphylococcus species, have developed mechanisms to survive such as biofilm formation, inactive forms and internalization. Therefore, radical debridement and specific antibiotics are necessary prior to reconstruction.

Keywords: educative; fracture treatment; nonunion; principals; review; strain theory

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Introduction

The 4th annual meeting of the Danish Orthopaedic Trauma Society was held from 5–6 April 2019 in Fredericia. This review contains a summary structured according to the lectures given by the different speakers describing the phenomenon of nonunion with all associated aspects.

Nonunion: the basics

Definition and the different types

A nonunion is a fracture that will not heal without further intervention. Although this is a pragmatic definition which very much depends on the evaluating surgeon, it provides the flexibility needed considering the variety of clinical presentations. Other descriptions focus more on the time aspect, defining a nonunion when there is no consolidation nine months post fracture and no radiographic progression of healing for three months.[1] Associated minor criteria include pain, impaired function, delayed rehabilitation resulting in a work and social handicap. A classification is needed to understand the problem and to form the basis for decision-making. A hypertrophic nonunion is stiff, has abundant callus and viable fracture fragments. Therefore, the biology is more than adequate, however, the mechanical instability prevents maturation and consolidation. An oligotrophic nonunion shows poor callus formation on X-ray, has viable fracture fragments and a disturbed local biology or mechanics. An atrophic nonunion is mobile, has no callus, non-viable bone or a bone defect which is caused by impaired biology, often combined with lacking mechanical stability. In contrast to a nonunion, a pseudarthrosis is a real false joint with an articular capsule leading to a non-physiological mobility. It is much more difficult to treat and usually requires resection before healing can be achieved. Based on this classification, the following conclusion may be drawn regarding the treatment strategy:

> *If the problem is mechanical, the solution is mechanical. If the problem is combined biologically and mechanically the solution is also combined.*

Unfortunately, it is not that simple, because there are other factors which need to be considered and which require a more holistic view on the issue. Host factors (such as age and sex), comorbidity (such as diabetes mellitus and vascular diseases), lifestyle aspects (such as smoking or drug abuse), certain medications and hormonal factors influence the incidence and treatment success in the same way as injury characteristics (such as location and soft tissue damage and contamination or infection).

Understanding the biomechanical reasons for nonunions

The degree of motion between the fracture parts is the key for healing. The interplay between biology and mechanics during fracture healing is complex and changes in one directly and indirectly affect the other. The study of this relationship is termed mechanobiology. During fracture healing, biological processes such as bone resorption and cellular differentiation and callus formation attempt to control the amount of fracture motion to within tolerable limits. The initial strain tolerance is up to 100% but as the initial callus becomes calcified, strain of only 2–10% is tolerated. If the movement within the fracture does not decrease over time no consolidation can be expected which results in a nonunion. Looking at the natural change, the contact area increases with callus formation leading to a decrease of motion. If the strain is > 10% (too much motion), only fibrous tissue can tolerate this amount of movement. Although the precise method of signal transduction has not yet been elucidated, mesenchymal (stromal) stem cells are found in the fracture gap percepting the mechanical conditions which determine their differentiation. The analysis of strain and interfragmentary movement leads to some conclusions which are not obvious at the outset. Small gap sizes under a relatively flexible configuration of locking plate fixation can cause excessive strain and fluid flow within the fracture site, resulting in fibrous tissue differentiation and delayed healing. By contrast, a relatively flexible locking plate fixation can improve cartilaginous callus formation and bone healing for larger gap sizes.[2] Furthermore, in segmental fractures the motion is distributed between several fracture lines resulting in a higher tolerance for motion, making these fractures prone to fixation with relative stability. Despite of this, complex fractures often take longer to heal, because comminution is also often associated with more tissue damage at the time of injury.

Simple fractures need absolute stability, multifragmentary fractures relative stability to prevent disturbed fracture healing. However, we should be aware of the fact that the basic mechanisms of direct fracture healing are only a model, and that callus formation is also observed following rigid fixation providing absolute stability especially on the opposite side of plate placement. With surgery we interfere with fracture healing, and the influence is negative when neglecting these principles. Sometimes the effects of an osteosynthesis are difficult to predict, leading to the development of ‘smarter implants’ measuring strain at the fracture site.[3] However, fixation devices sensing mechanical forces have not yet been introduced in daily clinical practice, just as potential biomarkers such as TGFβ have not.[4]

Epidemiology and which bones are at risk when fractured

In over 25 studies, the incidence of nonunions is reported to range between 5% and 10%.[5,6] However, they all refer to a textbook from the US published in the 1990s[7] which does not provide a reliable data source. The best current overview is provided by a Scottish study evaluating the risk of nonunions per fracture in a population of over 4 million adults.[8] Here, the overall risk of suffering from a nonunion was estimated to be 1.9% in adults, which is considerably less than previously believed. Age is a decisive influence, with the risk at 0.2% in children up to 14 years old (open growth plate) and 0.35% in teenagers up to 19 years old, which is significantly less than in adults.[9] Among adults, the risk for nonunion per fracture peaks between 25 and 45 years of age, declining thereafter. Correlating with this, osteoporosis and osteopenia were not identified as independent risk factors.[10] Male patients had a higher risk for nonunion which is likely caused by the fact that they more often suffer from high-energy trauma.

Table 1. Modified RUST score with a minimum of 4 and a maximum of 16 points

Points per cortex	Criteria
1	No callus
2	Callus present
3	Bridging callus
4	Remodelled

Among the different bones the risk is not equally distributed. It was highest in tibia fractures (5–6%) followed by clavicula (4–5%) and humerus (3%) fractures. Furthermore, the risk for nonunion was injury specific and increased in open fractures, and fractures following high-energy trauma with comminution.[11] Smoking,[12] alcohol abuse, HIV infection,[13] diabetes mellitus, renal failure and peripheral vascular diseases[14] enhanced the probability of sustaining bone-healing problems. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) also impaired fracture consolidation.[15]

How to diagnose a nonunion

The diagnosis of a nonunion is sometimes difficult. Both clinical and radiological criteria can be helpful. Typically, patients report inability to bear weight (84%), pain at fracture site (74%), and tenderness on palpation (38%).[16] Radiologically, the lack of callus seems to be more important than persistent fracture lines (75%). Computed tomography (CT) scanning can be supportive; however, the evaluation of the sometimes complex configuration can be difficult. Calori et al[17] suggested evaluating and quantifying the cross-sectional area, indicating the presence of a nonunion when bone bridging was less than 5% and considering the fracture healed when bridging was more than 25%. The frequently quoted statement that a fracture is radiologically stable when bone healing is present in three out of four cortices is doubtful, because it is based on an animal study with 21 rabbits and is not necessarily transferrable to humans.[18] Scoring systems provide a more systematic approach and were first introduced by Whelan et al,[19] presenting the RUST score evaluating status of consolidation of each cortical side of the bone. This was later modified by Litrenta et al[20] who developed the modified RUST score (Table 1) which may guide decision-making.

CT scanning can help; however, considering a specificity of only 62% it may be seen critically, because clefts in bone are of uncertain clinical importance, and there is a risk of operating on an already healed fracture.[21] In relation to this, Kleinlugtenbelt et al found in a rather small cohort no additional value for CT scanning compared to X-ray alone.[22] When in doubt how to treat a potential nonunion after evaluation of conventional radiographies then an additional CT scan usually leads to surgery.

Positron emission tomography (PET) or bone scintigraphy can support the diagnosis of infection and might help to determine the affected area; however, these imaging techniques are partially unsure, because the expected healing activity can give positive signals.

Although the decision for treating a nonunion is rather based on clinical symptoms and radiological findings, paraclinical features should be included in the diagnostic process. Basic blood values to check are calcium, vitamin D and parathyroid hormone. This recommendation is based on a study of 37 cases with nonunion in which 68% were diagnosed with vitamin D deficiency.[23] However, until now it could not be shown that vitamin D supplementation in deficiency situations improves outcome.[24] In case of continuous failure of treatment, phosphate, alkaline phosphatase, magnesium, cortisol, testosterone, and prolactin can be determined. A complete overview is provided by Nauth et al.[25] Comorbidity can be decisive to evaluate risk for failure. A typical example is diabetes mellitus increasing the risk for nonunion more than sevenfold.[26] This is important because the disease is unknown in some cases and can be improved. Therefore, measuring of glycosylated haemoglobin (HbA1c) is highly recommended when diagnosing delayed or failed fracture healing. Furthermore, the peripheral pulse status needs to be examined because arterial obstructive disease also raises the risk for disturbed bone consolidation. A summary of the essentials is provided in Table 2.

How to avoid nonunions: violation of principals of initial treatment

It is crucial to realize that principles of fracture treatment are there to be followed. Nonetheless, there are pitfalls, especially when the right principles are applied to the wrong indications. This chapter appreciates that complications are often a result of lack of planning, lack of knowledge, and sometimes lack of skills which can be trained. Typical errors are made regarding stability, reduction, handling of soft tissues, choice and placement of implants, and the lack of preoperative planning.

To avoid mistakes regarding stability, the nature of the fracture should be analysed clarifying which kind of stability is needed. Taking into account the mentioned theory of strain (change of length in relation to the total length at a given load),[27,28] direct healing occurs when strain is $<$ 2%, callus healing when strain is $>$ 2% but $<$ 10% and a nonunion when strain remains $>$ 10%. The conclusions for fixation are straightforward: Simple fractures need absolute stability. Complex fractures need relative stability. However, absolute stability is not the same thing as strength! Therefore, lag-screw fixation is usually combined with a plate for neutralization of leverage and forces. The placement of the plate also plays a decisive role, because it should encounter the bending direction[29]

Table 2. Checklist for diagnostic and analytic procedures in case of nonunion

Classification (atrophic, oligotrophic, hypertrophic)
- Evaluation of stability
- Evaluation of local biology
Identification of injury-related problems
- Anatomic location
- Malalignment
- Soft tissue coverage
- Bending site
Check for infection
- Systemic and local clinical symptoms
- Serum parameters
Check for systemic reasons
- Calcium
- Vitamin D
- Parathyroid hormone
- HbA1c

and, consequently, counteract dislocating forces. While distal tibia fractures can be malaligned in a valgus or varus position, the bending side of the femur is usually lateral caused by the femoral neck which directs the force vector over the medial side. However, it is important not only to reflect on the bone but also the ligaments and tendon insertions. The approach used should therefore consider both the standard anatomy and also the individual soft tissue situation of the patient. Although it is possible that in some hospitals plating might be the standard of care for certain locations, an open fracture might drive the decision to deviate from this standard and use a frame instead. Although diaphyseal fractures do not need anatomical reduction but reconstruction of axis, length and rotation, a lack of reduction can prevent fracture healing. A gap is a risk but should be analysed in light of strain theory. This could mean that, in complex fractures, gaps can be tolerated because the forces are distributed over several fragments, leaving the strain below 10%. This is of course only possible when applying relative stability.

Most failures are avoidable and explainable, which is why preoperative planning is definitely recommended. Also, when a fracture has failed to heal a critical analysis is required and the same mistakes should not be repeated. Problems with nonunions are frequently the same as those related to normal fractures such as varus malalignment in proximal femur fractures or disturbed rotation in forearm fractures.

Goals of treatment and basic treatment strategy

Although the treatment of nonunions includes different strategies with different levels of evidence, there are key issues which always need to be considered: the patient, patient's expectations, and principles of treatment with individual adaptions. The treatment should generally aim for a reduction of symptoms such as pain and swelling, and improvement of function. For a minority of patients this might mean that an amputation or a 'stable' nonunion with acceptable pain level might be an option. For most patients an operative revision is indicated and required when progress in healing is not expected without further intervention, or if healing will result in a significant malalignment. Again, we must stress strain theory,[30] because a reduction of the quotient Δ length/length applying a certain load is required to treat a nonunion. This can be achieved by reducing the external load, a correction of axis (which also reduces the load), and by reducing the interfragmentary strain. Although treatment of nonunions is mainly to improve the biomechanical situation, biological stimulation is also required. A variety of techniques are described such as autograft (gold standard), bone transport,[31] Masquelet technique,[32] osteoinductive proteins such as bone morphogenetic protein 2 or 7,[33] mechanobiology,[34] vascularized bone graft[35] or a free flap (vascularity).[36]

The kind of fixation is not decisive, it is the whole concept considering the treatment of problems regarding soft tissue, local biology and stability which determines the applied osteosynthesis.

Briefly, the five pillars of nonunion management of the mechanobiological concept are mentioned: optimization of modifiable risk factors, mechanical alignment, stable fixation, mechanobiological stimulation, and early functional rehabilitation.[37]

Patient factors that can be influenced or paused are smoking, diabetes control, antiretroviral therapy for HIV infection, anaemia, malnutrition, vitamin D, use of NSAIDs, steroids, methotrexate, and biological anti-rheumatoid therapy. This concept requires stabilization with a circular fixator which is safe and effective considering 93% of unions after one operation and a total success rate of 98% with final bone union.[34,37] Another advantage is the opportunity to apply biological stimulation over time because the axis can be corrected slowly or stepwise. Mobile and stiff nonunions can be addressed right away and closed. Furthermore, bone defects can first be shortened and later undergo lengthening with the same implant. In contrast, all concepts using internal fixation demand stable soft tissues and a 'one-shot' or two-stage correction. A typical example is the 'diamond concept',[38] building up on the following basic cornerstones: osteoconductive scaffolds, growth factors, a stable and possibly bactericidal environment, osteogenic cells and sufficient vascularity. The current published success rate is 84%; however, no comparing studies have been carried out analysing the effectiveness of different concepts. Since these are complex treatment methods demanding different disciplines and a whole environment including schooled nursing staff and physiotherapists, the set-up of a comparing clinical trial would be very difficult.

Table 3. The Calori nonunion scoring system (NUSS)

Score	Recommended measures
< 25	Autograft, intramedullary nailing, plating
25–75	Circular fixation, vascularized bone graft, free flap, BMPs, bone transport
> 75	Amputation

Considering all the parameters influencing the decision, a scoring system has been suggested to direct treatment.[17] Fifteen parameters for bone (highest impact), soft tissue, and patient conditions are evaluated resulting in the Calori nonunion scoring system (NUSS) ranging from 0 to 100.Table 3 indicates the recommended measures dependent on the score which was recently validated.[39]

Specific treatment of nonunions

There is no rule that a nonunion always has to be treated with a certain implant apart from the more universal use of frames when the principles are respected. Still, there are some considerations that apply to specific implant groups which are now elaborated more in detail.

Nonunion treated with intramedullary nails

Nailing often can provide stable fixation, and stable fixation is the best fixation. An osteosynthesis with intramedullary nails is associated with a limited soft tissue insult, combines stability with load sharing, and allows early weight bearing and rehabilitation. Reaming does not only increase stability by enlarging the contact area between nail and bone, it also leads to enhanced reactive periosteal blood supply after temporary destruction of the endosteal structures. Issues related to this fixation method are the sometimes difficult access to the medullary canal, the limited deformity correction and the predominantly restricted use in diaphyseal regions. Indications were recently extended with introduction of lengthening with nails allowing to address larger defects.[40] Formerly, infected nonunions could not be treated using nails; however, this has changed to a certain degree after the introduction of antibiotic-coated nails.[41] Handmade cement-covered nails loaded with antibiotics are also an option (Fig. 1).[42,43] Dynamization, describing the removal of interlocking bolts for induction of axial compression, is a possibility to support bone healing. Although one study demonstrated a success rate of 83% in tibial nonunion management,[20] further data supporting this technique are very limited. It destabilizes the nail, and timing is doubtful. Therefore, the exchange of the nail is rather recommended. It allows a larger nail to be inserted providing increased stability following medullary reaming which also improves the local biology as mentioned above. Though there are only cohort studies available, data indicate a success rate of about 90%.[20] The procedure of reaming is associated with an increase in cortical temperature and embolic phenomena which was much improved with the newer reaming systems with less pressure and better drainage.[44] Since unreamed nailing was associated with more technical complications, and there was no difference regarding the incidence of adult respiratory distress syndrome or death, reaming is generally recommended.[45,46] Fig. 2 shows an example in which a nonunion occurred after plating.

Fig. 1 Intramedullary nail for infected situations. Individually manufactured cement-coated nail loaded with antibiotics.

Nonunion treated with external fixators

External fixation is another option to treat nonunions, not contradicting nails or plates. However, it offers good options especially when patients are referred late, already have joint contractures, severe deformities, a bad compliance, and are dissatisfied with first-line treatment.

External fixation using frames allows function to be improved rather than only maintained. The principals (the five pillars of nonunion management) were discussed in section “Goals of treatment and basic treatment strategy” introducing the mechanobiological effect. Therefore, framing may be considered as the only true biologic fixation. It is extremely effective resulting in a

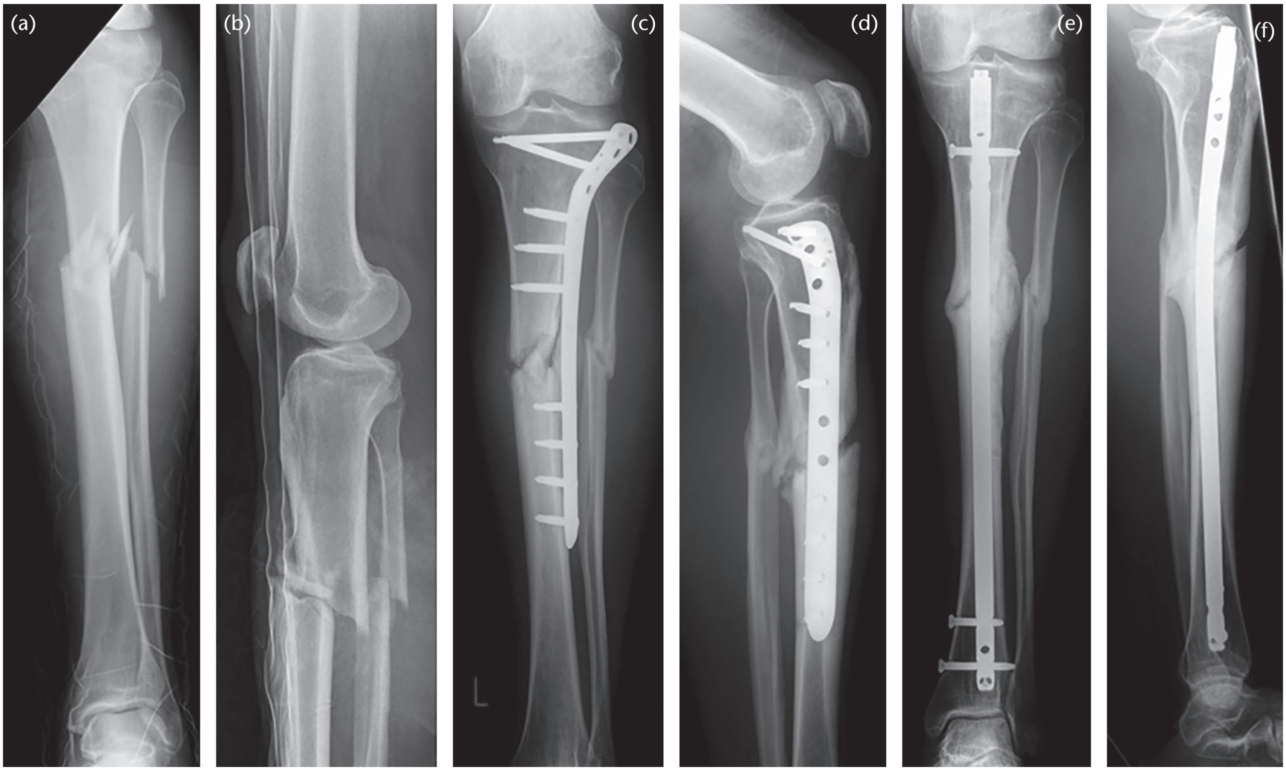

Fig. 2 Intramedullary nail to treat a nonunion. (a) and (b) show a fracture of the lower leg between the proximal and the middle third. The tibia was initially stabilized using a LISS (less-invasive stabilization system) reconstructing axis, length and rotation but lacking compression and leaving a gap. (c) and (d) show the situation after six months with a persisting fracture line. The patient presented with pain while bearing weight. The inserted nail provided stability, biology after reaming and was used to compress by striking back after distal locking as shown. The proximal dynamic locking option was used. (e) and (f) demonstrate sufficient callus formation and bone bridge after three months, the patient was pain-free.

union rate of > 90%[34,37] and was first recognized in Western literature in the 1990s. These devices decrease strain in high-strain nonunions by adding stability and fracture distraction. This technique allows simultaneous correction of the mechanical axis as well as manipulation of the mechanical environment to promote bone formation (Fig. 3). It is important to discriminate between stiff and mobile nonunions because this determines how to correct – immediate or slowly, and open or closed. A ring fixator provides less stability in oblique fracture lines which can be improved using olive wires to reduce shear forces, or by an osteotomy making the fractures more complex and distributing the strain. Additive measures need to accompany correction with frames. This could be a fibula osteotomy to release options for correction, or other measures to keep joint function, such as tendon lengthening. Hexapod circular external fixators are extremely accurate at correcting deformities in three dimensions; however, there are differences when using different models such as Taylor Spatial Frame or TrueLok-Hex methods, resulting in variations of translational measurements for both deformity and mounting parameters. These differences must be appreciated in order to effectively use these systems.[47]

When to use plate fixation and how

The initial strain environment is relatively low in multifragmentary fractures. As the fracture starts to unite, the various fragments heal to each other, eventually leaving a single fracture line with higher strain. If the focal strain remains low enough, uneventful healing will occur. However, if the focal strain at the last fracture line is above the threshold for bone formation, healing will stop.

Complex fractures turn into simple nonunions. Therefore, absolute stability is needed, which can be realized with lag screws, compression plates or compression devices (Fig. 4). Especially in oblique configurations of nonunions the plate can provide better stability than other devices. According to the defined principals, the reasons for failure must be analysed and the plan for treatment needs to consider correction of malalignment and stability. Soft tissue is a more immanent issue compared to external fixation devices, because a plate needs coverage and should safely tolerate the surgical approach.

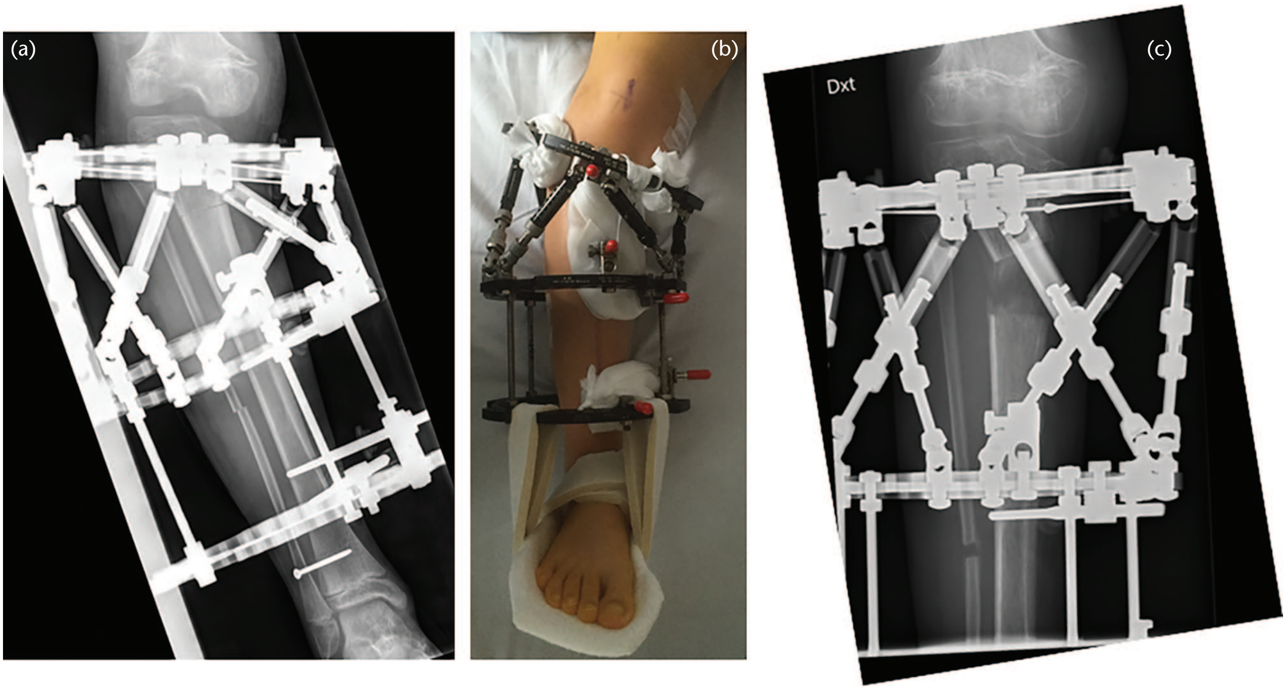

Fig. 3 Taylor Spatial Frame for correction of malalignment and distraction osteogenesis. (a) and (b) show the clinical situation with varus malalignment of the lower leg and assembled Taylor Spatial Frame. (c) demonstrates sufficient healing and correct alignment after lengthening.

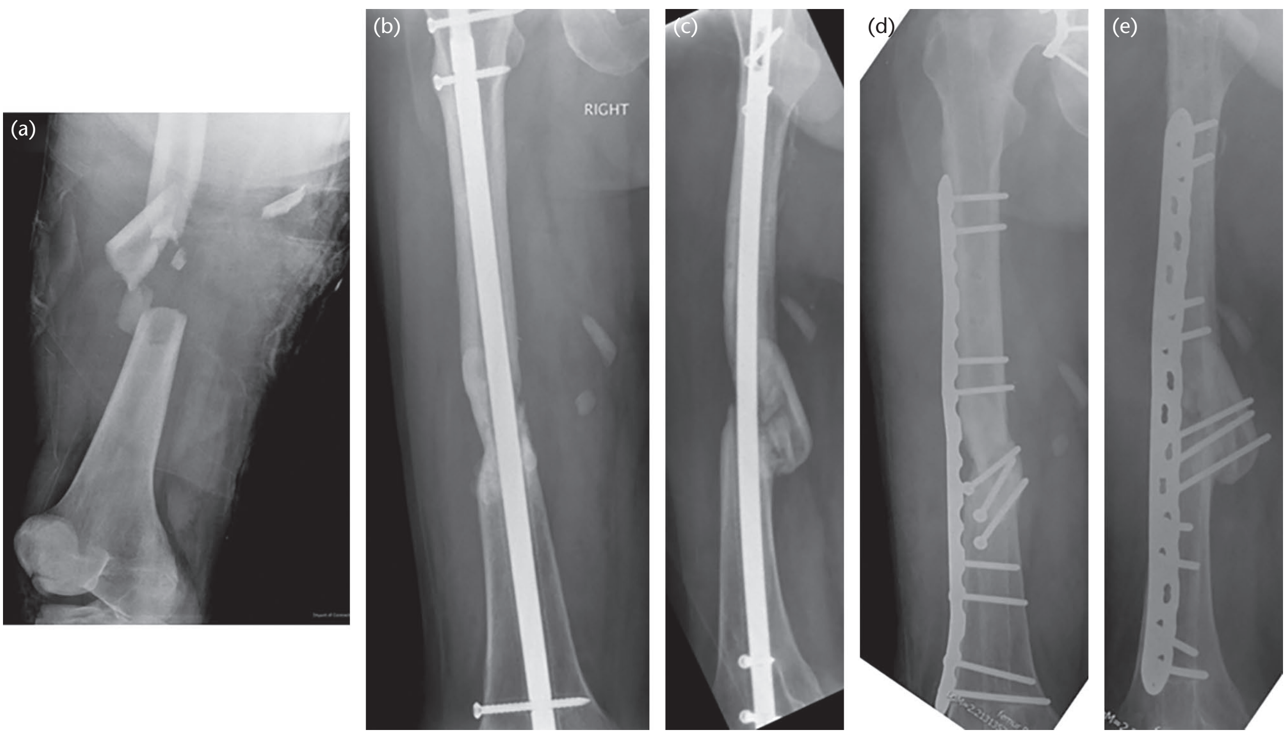

Fig. 4 Plating to treat nonunions. (a) shows an AO-type 32-C3 fracture stabilized with a nail. After six months, the initially complex fracture turned into a simple nonunion as demonstrated in (b) and (c). Applying absolute stability with lag screws buttressed by a plate, the nonunion healed after three months as shown in (d) and (e).

Is grafting necessary and if so, which options are available?

The need for a graft depends on the applied treatment strategy in which the presence of a significant bone defect is decisive.[30] A graft not only fills the gap but provides biology making it a useful adjuvant mainly in atrophic Nonunions.[25] Currently, the autograft may be considered as the gold standard. The initial treatment concept determines necessity, time point, nature and location of application. While the Masquelet technique always requires bone graft for filling the defect, bone transports often need the graft only at the docking site. In contrast, mechanobiological strategies usually can abstain from using grafts at all. There are only rare cases when grafting may be considered as a single intervention. An example is an open fracture which is initially stably fixed by a nail with a gap because of bone loss. Here, scheduled grafting after exclusion of infection can be an option. Other successful techniques have been described to stimulate bone growth as mentioned in passage "Goals of treatment and basic treatment strategy" taking effect by one or more of the four basic principles osteogenesis, osteoinduction, osteoconduction,[48] and osteostimulation.[49] Osteogenesis means bone formation by viable cells provided by bone marrow or bone autograft. Osteoinduction describes bone formation at extra-skeletal sites by mitogenesis of undifferentiated perivascular mesenchymal stromal cells, leading to the formation of osteoprogenitor cells and osteoblasts.[50] This is seen following transplantation of autograft, bone marrow, demineralized bone matrix, bone morphogenetic proteins (BMPs), platelet-rich plasma, and autologous growth factors. Osteoconduction is a process of enhanced bone formation due to a suitable structural environment where the osteoconductive material serves as a passive scaffold.[51] This is observed after transplantation of autograft or allograft bone substitutes (demineralized bone matrix, calcium phosphate cement, hydroxyapatite, trabecular metal, tricalcium phosphate). Osteostimulation was recently pointed out as being a separate process supporting bone healing in which osteoblast proliferation and differentiation are actively stimulated. The idea is to attenuate the proinflammatory processes through an ionic exchange, balancing pH and creating a scaffolding environment through which new bone forms.[52] Increased levels of DNA synthesis and of the osteoblast markers osteocalcin and alkaline phosphatase could be measured following implantation of bioglass.[53]

Before grafting, the defect size and soft tissue coverage should be evaluated and alternatives such as shortening considered. The iliac crest was, for a long period, the first choice for harvesting; however, the reamer-irrigator-aspirator (RIA) became more and more popular as a device for bone graft harvesting. With this, the material is collected from the femur canal. A recent study showed that RIA graft is just as potent to support healing as bone from the iliac crest. The RIA technique was associated with significantly less donor-site pain and yielded in a greater volume.[54] Nevertheless, the literature also mentions some specific problems with using RIA, such as the limited selection of reamer sizes, femoral neck fractures and infections.[55] An alternative to bone graft is the off-the-shelf use of BMPs. In a prospective, randomized, controlled, multicentre trial including 124 tibial nonunions with a follow-up of nine months, OP-1 (BMP-7) used with type I bovine collagen was just as effective as autograft.[56] Similarly, non-inferiority could be demonstrated for BMP-2 in the treatment of bone defects.[57] After BMP-2 failed to show improved effects compared to standard of care treatment in open and closed tibia fractures,[58,59] it was used more cautiously. Furthermore, the current availability of BMPs is doubtful and a recent study raised concerns regarding an underestimation of possible side effects.[60] Although allograft has osteoconductive properties it is usually used more to expand the transplanted bone volume after mixing it with autograft. Newer approaches such as the local injection of allogenic stem cells still have an experimental status.

Management of the infected nonunion

Twenty per cent of aseptic nonunions have positive intraoperative cultures, indicating that the problem of infection for the pathogenesis of failed fracture healing is underestimated.[38] If typical symptoms such as redness, swelling and fever are present, the infection is acute and the clinical diagnosis rather simple. However, frequently delayed or failed fracture consolidation is associated with low-grade and chronic infections which are often difficult to recognize. Several mechanisms contribute to this phenomenon such as biofilm formation,[61] survival of bacteria in inactive forms, and internalization of bacteria.[62] This allows the infection to persist and to become reactivated in times of a suppressed immune system. Radiographic changes are lysis, loosening, sequestering, and periostitis. Magnet resonance imaging (MRI) is very sensitive but limited by artefacts around the implant. PET/CT may effectively distinguish between infected nonunion, aseptic nonunion, soft tissue infection and chronic osteomyelitis[63] and has an estimated sensitivity of 95% and a specificity of 87%. Similar results were shown for white blood cell (WBC) scintigraphy with a sensitivity of 79%, and a specificity of 97%.[64] Single-photon emission computed tomography (SPECT)/CT scan is another possibility for testing, with a low sensitivity but good specificity for infection and non-viability of the nonunion site.[65] However, data are preliminary.[66] As an additional risk factor, infection is part of the scoring system by Calori described above.[17] The principals of treatment almost follow the guidelines of cancer treatment and tumour surgery; this means that

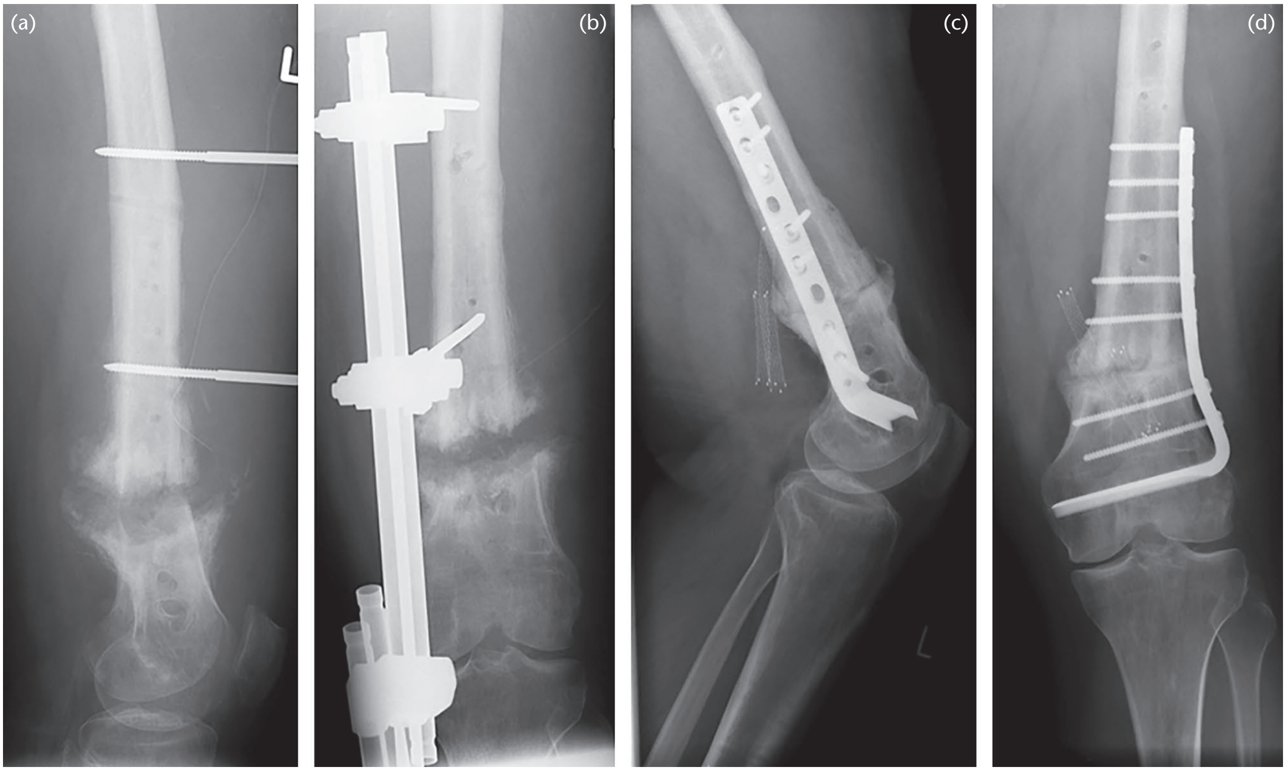

Fig. 5 Infected nonunion. Treatment of a staphylococcus aureus infected nonunion in a 31-year-old male. (a) and (b) show the status after implant removal with debridement, local antibiotics plus external fixation. (c) and (d) depict the situation after resection, and compression plating. Debridement should be rigorous but careful. Intraoperative lesion of the femoral artery treated by a vascular endoprosthesis.

tissue and bone with signs of infection should radically be removed. After infection is sufficiently treated, bone and soft tissue are reconstructed using the described methods such as autograft or bone transport. A successful adjuvant in soft tissue management is negative-pressure wound therapy (NPWT), providing a chance to preserve the implant in 44% and leading to successful healing in 73% of cases.[67] Typically, infections are caused by staphylococcus species, because these bacteria are skin commensals, have certain affinity mechanisms for host proteins (especially staph. aureus) binding exposed bone collagen, produce enzymes allowing invasion, can survive as an inactive 'L' form, and are biofilm producers. Calculated antibiotic treatment should therefore always cover this spectrum of bacteria. However, the species diversity of chronic infection is large, and a targeted antibiotic treatment should start as early as possible. A recent clinical trial pointed out that oral antibiotic therapy was non-inferior to intravenous antibiotic therapy when used during the first six weeks for complex orthopaedic infection.[68] Although there is a lack of evidence, the use of local antibiotics is recommended, both because of high local concentrations and less systemic side effects.[69] Soft tissue management is even more important in infected nonunion, because the immune defence is only functioning on the basis of a sufficiently covered bone. Furthermore, patient factors need to be optimized with high priority. Debridement and resection lead to defects which are also called 'dead space'. Since this can develop into a niche for bacteria, it needs to be managed and filled. A mentioned alternative is shortening. Moreover, McNally et al reported on a single-stage protocol using a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite which was effective in the treatment of chronic osteomyelitis.[70] It offers a more patient-friendly treatment compared with other options and can also be used in two-stage procedures. Until now, no differences in success rates for single- or two-stage procedures could be found.[71] Fig. 5 shows an example of a two-stage procedure treating a nonunion of the distal femur shaft.

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REFERENCES

1. **Calori GM, Mazza EL, Mazzola S, et al.** Non-unions. *Clin Cases Miner Bone Metab* 2017;14:186–188.

2. **Miramini S, Zhang L, Richardson M, Mendis P, Oloyede A, Ebeling P.** The relationship between interfragmentary movement and cell differentiation in early fracture healing under locking plate fixation. *Australas Phys Eng Sci Med* 2016;39:123–133.

3. **Ledet EH, Liddle B, Kradinova K, Harper S.** Smart implants in orthopedic surgery, improving patient outcomes: a review. *Innov Entrep Health* 2018;5:41–51.

4. **Zimmermann G, Henle P, Küsswetter M, et al.** TGF-beta1 as a marker of delayed fracture healing. *Bone* 2005;36:779–785.

5. **Dijkman BG, Sprague S, Bhandari M.** Low-intensity pulsed ultrasound: nonunions. *Indian J Orthop* 2009;43:141–148.

6. **Giannoudis PV, Tzioupis C.** Clinical applications of BMP-7: the UK perspective. *Injury* 2005;36:S47–S50.

7. **Praemer A, Furner S, Rice DP.** *Musculoskeletal conditions in the United States*. Rosemont, IL: American Academy of Orthopaedic Surgeons, 1999, 2nd revised edition.

8. **Mills LA, Aitken SA, Simpson AHRW.** The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults. *Acta Orthop* 2017;88:434–439.

9. **Mills LA, Simpson AH.** The risk of non-union per fracture in children. *J Child Orthop* 2013;7:317–322.

10. **van Wunnik BPW, Weijers PHE, van Helden SH, Brink PRG, Poeze M.** Osteoporosis is not a risk factor for the development of nonunion: a cohort nested case-control study. *Injury* 2011;42:1491–1494.

11. **Kubosch EJ, Bernstein A, Wolf L, Fretwurst T, Nelson K, Schmal H.** Clinical trial and in-vitro study comparing the efficacy of treating bony lesions with allografts versus synthetic or highly-processed xenogeneic bone grafts. *BMC Musculoskelet Disord* 2016;17:77.

12. **Pearson RG, Clement RGE, Edwards KL, Scammell BE.** Do smokers have greater risk of delayed and non-union after fracture, osteotomy and arthrodesis? A systematic review with meta-analysis. *BMJ Open* 2016;6:e010303.

13. **Gardner ROE, Bates JH, Ng'oma E, Harrison WJ.** Fracture union following internal fixation in the HIV population. *Injury* 2013;44:830–833.

14. **Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, et al.** Epidemiology of fracture nonunion in 18 human bones. *JAMA Surg* 2016;151:e162775.

15. **Richards CJ, Graf KW Jr, Mashru RP.** The effect of opioids, alcohol, and nonsteroidal anti-inflammatory drugs on fracture union. *Orthop Clin North Am* 2017;48:433–443.

16. **Bhandari M, Fong K, Sprague S, Williams D, Petrisor B.** Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. *J Bone Joint Surg Am* 2012;94:e1091–e1096.

17. **Calori GM, Colombo M, Mazza EL, et al.** Validation of the non-union scoring system in 300 long bone non-unions. *Injury* 2014;45:S93–S97.

18. **Panjabi MM, Walter SD, Karuda M, White AA, Lawson JP.** Correlations of radiographic analysis of healing fractures with strength: a statistical analysis of experimental osteotomies. *J Orthop Res* 1985;3:212–218.

19. **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* 2010;68:629–632.

20. **Litrenta J, Tornetta P III, Vallier H, et al.** Dynamizations and exchanges: success rates and indications. *J Orthop Trauma* 2015;29:569–573.

21. **Bhattacharyya T, Bouchard KA, Phadke A, Meigs JB, Kassarjian A, Salamipour H.** The accuracy of computed tomography for the diagnosis of tibial nonunion. *J Bone Joint Surg Am* 2006;88:692–697.

22. Kleinlugtenbelt YV, Scholtes VAB, Toor J, et al. Does computed tomography change our observation and management of fracture non-unions? *Arch Bone Jt Surg* 2016;4:337–342.

23. Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. *J Orthop Trauma* 2007;21:557–570.

24. Haines N, Kempton LB, Seymour RB, et al. The effect of a single early high-dose vitamin D supplement on fracture union in patients with hypovitaminosis D: a prospective randomised trial. *Bone Joint J* 2017;99-B:1520–1525.

25. Nauth A, Lee M, Gardner MJ, et al. Principles of nonunion management: state of the art. *J Orthop Trauma* 2018;32:S52–S57.

26. Gortler H, Rusyn J, Godbout C, Chahal J, Schemitsch EH, Nauth A. Diabetes and healing outcomes in lower extremity fractures: a systematic review. *Injury* 2018;49:177–183.

27. Perren SM. Evolution of the internal fixation of long bone fractures: the scientific basis of biological internal fixation: choosing a new balance between stability and biology. *J Bone Joint Surg Br* 2002;84:1093–1110.

28. Perren SM. Physical and biological aspects of fracture healing with special reference to internal fixation. *Clin Orthop Relat Res* 1979;138:175–196.

29. Gautier E, Perren SM, Cordey J. Effect of plate position relative to bending direction on the rigidity of a plate osteosynthesis: a theoretical analysis. *Injury* 2000;31:C14–C20.

30. Elliott DS, Newman KJH, Forward DP, et al. A unified theory of bone healing and nonunion: BHN theory. *Bone Joint J* 2016;98-B:884–891.

31. Napora JK, Weinberg DS, Eagle BA, Kaufman BR, Sontich JK. Hexapod stacked transport for tibial infected nonunions with bone loss: long-term functional outcomes. *J Orthop Trauma* 2018;32:e12–e18.

32. El-Hadidi TT, Soliman HM, Farouk HA, Radwan MAE. Staged bone grafting for the management of segmental long bone defects caused by trauma or infection using induced-membrane technique. *Acta Orthop Belg* 2018;84:384–396.

33. Govender S, Csimma C, Genant HK, et al; BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. 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.

34. Ferreira N, Marais LC, Aldous C. Mechanobiology in the management of mobile atrophic and oligotrophic tibial nonunions. *J Orthop* 2015;12:S182–S187.

35. Rahimnia A, Rahimnia A-H, Mobasher-Jannat A. Clinical and functional outcomes of vascularized bone graft in the treatment of scaphoid non-union. *PLoS One* 2018;13:e0197768.

36. Guzzini M, Lanzetti RM, Perugia D, et al. The treatment of long bones nonunions of upper limb with microsurgical cortico-periosteal free flap. *Injury* 2017;48:S66–S70.

37. Ferreira N, Marais LC. Management of tibial non-unions according to a novel treatment algorithm. *Injury* 2015;46:2422–2427.

38. Moghaddam A, Thaler B, Bruckner T, Tanner M, Schmidmaier G. Treatment of atrophic femoral non-unions according to the diamond concept: results of one- and two-step surgical procedure. *J Orthop* 2016;14:123–133.

39. Abumunaser LA, Al-Sayyad MJ. Evaluation of the Calori et al nonunion scoring system in a retrospective case series. *Orthopedics* 2011;34:359.

40. Bolbasov EN, Popkov DA, Kononovich NA, Gorbach EN, Khlusov IA, Golovkin AS, et al. Flexible intramedullary nails for limb lengthening: a comprehensive comparative study of three nails types. *Biomed Mater* 2019;14:025005

41. Metsemakers WJ, Reul M, Nijs S. The use of gentamicin-coated nails in complex open tibia fracture and revision cases: a retrospective analysis of a single centre case series and review of the literature. *Injury* 2015;46:2433–2437.

42. Cho J-W, Kim J, Cho W-T, Kent WT, Kim H-J, Oh J-K. Antibiotic coated hinged threaded rods in the treatment of infected nonunions and intramedullary long bone infections. *Injury* 2018;49:1912–1921.

43. Helbig L, Bechberger M, Aldeeri R, et al. Initial peri- and postoperative antibiotic treatment of infected nonunions: results from 212 consecutive patients after mean follow-up of 34 months. *Ther Clin Risk Manag* 2018;14:59–67.

44. Klein C, Sprecher C, Rahn BA, Green J, Müller CA. Unreamed or RIA reamed nailing: an experimental sheep study using comparative histological assessment of affected bone tissue in an acute fracture model. *Injury* 2010;41:S32–S37.

45. Tornetta P III, Tiburzi D. The treatment of femoral shaft fractures using intramedullary interlocked nails with and without intramedullary reaming: a preliminary report. *J Orthop Trauma* 1997;11:89–92.

46. Tornetta P III, Tiburzi D. Antegrade or retrograde reamed femoral nailing: a prospective, randomised trial. *J Bone Joint Surg Br* 2000;82:652–654.

47. Ferreira N, Birkholtz F. Radiographic analysis of hexapod external fixators: fundamental differences between the Taylor Spatial Frame and TrueLok-Hex. *J Med Eng Technol* 2015;39:173–176.

48. Kostenuik P, Mirza FM. Fracture healing physiology and the quest for therapies for delayed healing and nonunion. *J Orthop Res* 2017;35:213–223.

49. Xu A, Zhuang C, Xu S, et al. Optimized bone regeneration in calvarial bone defect based on biodegradation-tailoring dual-shell biphasic bioactive ceramic microspheres. *Sci Rep* 2018;8:3385.

50. Calcei JG, Rodeo SA. Orthobiologics for bone healing. *Clin Sports Med* 2019;38: 79–95.

51. Murahashi Y, Yano F, Nakamoto H, et al. Multi-layered PLLA-nanosheets loaded with FGF-2 induce robust bone regeneration with controlled release in critical-sized mouse femoral defects. *Acta Biomater* 2019;85:172–179.

52. Rectenwald JE, Minter RM, Rosenberg JJ, Gaines GC, Lee S, Moldawer LL. Bioglass attenuates a proinflammatory response in mouse peritoneal endotoxicosis. *Shock* 2002;17:135–138.

53. Wei L, Ke J, Prasadam I, et al. A comparative study of Sr-incorporated mesoporous bioactive glass scaffolds for regeneration of osteopenic bone defects. *Osteoporos Int* 2014;25:2089–2096.

54. Dawson J, Kiner D, Gardner W II, Swafford R, Nowotarski PJ. The reamer-irrigator-aspirator as a device for harvesting bone graft compared with iliac crest bone graft: union rates and complications. *J Orthop Trauma* 2014;28:584–590.

55. Han F, Peter L, Lau ETC, Thambiah J, Murphy D, Kagda FHY. Reamer irrigator aspirator bone graft harvesting: complications and outcomes in an Asian population. *Injury* 2015;46:2042–2051.

56. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. *J Bone Joint Surg Am* 2001;83-A (Pt 2):S151–S158.

57. Jones AL, Bucholz RW, Bosse MJ, et al; BMP-2 Evaluation in Surgery for Tibial Trauma-Allgraft (BESTT-ALL) Study Group. Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects: a randomized, controlled trial. *J Bone Joint Surg Am* 2006;88:1431–1441.

58. Lyon T, Scheele W, Bhandari M, et al. Efficacy and safety of recombinant human bone morphogenetic protein-2/calcium phosphate matrix for closed tibial diaphyseal fracture: a double-blind, randomized, controlled phase-II/III trial. *J Bone Joint Surg Am* 2013;95:2088–2096.

59. 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.

60. James AW, LaChaud G, Shen J, et al. A review of the clinical side effects of bone morphogenetic protein-2. *Tissue Eng Part B Rev* 2016;22:284–297.

61. Zimmerli W. Clinical presentation and treatment of orthopaedic implant-associated infection. *J Intern Med* 2014;276:111–119.

62. Arciola CR, Hänsch GM, Visai L, et al. Interactions of staphylococci with osteoblasts and phagocytes in the pathogenesis of implant-associated osteomyelitis. *Int J Artif Organs* 2012;35:713–726.

63. Shemesh S, Kosashvili Y, Groshar D, et al. The value of 18-FDG PET/CT in the diagnosis and management of implant-related infections of the tibia: a case series. *Injury* 2015;46:1377–1382.

64. Govaert GAM, Bosch P, IJpma FFA, et al. High diagnostic accuracy of white blood cell scintigraphy for fracture related infections: results of a large retrospective single-center study. *Injury* 2018;49:1085–1090.

65. Liodakis E, Liodaki E, Krettek C, et al. Can the viability of a nonunion be evaluated using SPECT/CT? A preliminary retrospective study. *Technol Health Care* 2011;19:103–108.

66. Madsen JL. Bone SPECT/CT detection of a sequestrum in chronic-infected nonunion of the tibia. *Clin Nucl Med* 2008;33:700–701.

67. Izadpanah K, Hansen S, Six-Merker J, Helwig P, Südkamp NP, Schmal H. Factors influencing treatment success of negative pressure wound therapy in patients with postoperative infections after Osteosynthetic fracture fixation. *BMC Musculoskelet Disord* 2017;18:247.

68. Li H-K, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med* 2019;380:425–436.

69. Kühn K-D, Renz N, Trampuz A. [Local antibiotic therapy]. *Unfallchirurg* 2017;120:561–572.

70. McNally MA, Ferguson JY, Lau ACK, et al. Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite: a prospective series of 100 cases. *Bone Joint J* 2016;98-B:1289–1296.

71. Struijs PAA, Poolman RW, Bhandari M. Infected nonunion of the long bones. *J Orthop Trauma* 2007;21:507–511.