infection when definitive fixation overlapped pin sites, compared to 10% when it did not; a statistically significant increase [11].

Roussignol et al. performed a retrospective review of 55 patients treated with ex-fix and secondary IMN after traumatic tibial shaft fractures (16 closed, 39 open). Of note, they also excluded patients with external fixator pin site infections. They analyzed time to IMN (mean 9 +/-9.6 weeks), acute or delayed exchange (23 acute vs. 32 staged, mean 12-day interval), culture results of reaming products, post-IMN infection and time to union. There were four septic complications and one aseptic nonunion requiring re-nailing. Acute versus delayed IMN did not correlate with increased infection risk, with only open fracture grade correlating with infection risk, and the union rate was 96%. Based on these results, they therefore recommend acute (one-stage) exchange of ex-fix for IMN [12]. Bhandari et al. performed a literature review on ex-fix conversion to IMN in tibia and femur fractures, including one level II study and the remainder level IV studies. They looked at studies with planned conversion from ex-fix to IMN, and those where IMN was used to salvage failed treatment with ex-fix. In 6 studies totaling 185 patients for planned conversion for femur fracture, with a mean 10 days ex-fix and 1 day interval to IMN, the infection rate was 2.6%. For tibias, 9 studies on planned conversion (n = 268) averaged 8.6% infection and 92% union, with shorter ex-fix time (< 28 days) correlating with an 83% reduction in the risk of infection compared to > 28 days [8].

Regarding time in ex-fix, Monni et al. reported a mean ex-fix time of 185 days (range 61-370), with poor outcomes correlating with longer time [7]. Bhandari et al. performed a meta-analysis assessing when to perform conversion, with deep infection rates 83% lower when IMN was performed within 28 days compared to after 28 days [8]. These studies both suggest earlier conversion is preferable. However, Yokoyama et al. performed multivariate analysis of 42 cases of secondary IMN after open lower leg fracture treated with initial ex-fix, with 7 (16.7%) developing deep infection, and found only time to skin coverage, with a threshold of 1 week, was significantly correlated with deep infection. They did not find a relationship between infection and the duration of ex-fix (</= or > 3 weeks), the interval between ex-fix removal and IMN (</= or > 2 weeks), or the existence of superficial infection or pin tract infection [13]. Similarly, Roussignol et al. did not find a correlation between infection risk and time in ex-fix before IMN [7].

While most studies have excluded patients with active pin site infections, Yokoyama et al. did not find a relationship between superficial infection or pin tract infection and rates of deep infection after IMN [13].

Regarding timing of soft tissue coverage, the previously cited Yokoyama et al. noted restoration of soft tissue coverage within one week correlated with a decreased risk of infection [13]. Outside of external to internal fixation conversion, other literature has used the threshold of five days from initial injury to wound closure before rates of wound healing complications and infections increase [9]. Most orthopaedic literature supports earlier soft tissue coverage in open fractures as protective against infection, irrespective of fixation type [14].

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## QUESTION 7: What are the alternatives to segmental resection in septic non-union?

**RECOMMENDATION:** Surgical alternatives to segmental resection include bone grafting, unroofing, decortication, distraction osteogenesis or intramedullary reaming to address the site of osteomyelitis. All dead bone and soft tissue should be removed.

**LEVEL OF EVIDENCE:** Limited

**DELEGATE VOTE:** Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

### RATIONALE

Operative debridement of necrotic tissue has been a surgical principle of infection treatment for centuries. Reports from the 1960s demonstrated that it is sometimes possible to heal a fracture nonunion with bone grafting and stabilization without disruption of the non-united bone site [1]. However, failures were common and continued infection was an expected outcome. In 1984, Cierny et al. published a classification of osteomyelitis and described both an anatomic description of the site of infection and a description of the host with recommendations for debridement strategy [2].The fundamental principle is debridement of all dead and infected bone in the same manner that a malignancy would be treated with a marginal excision.

Cierny's guidelines are that infection involving only the medullary canal can be potentially treated with reaming or a reamer-irrigator aspirator (RIA) to achieve adequate debridement. More localized infection can be treated with unroofing or decortication of the bone segments. However, diffuse infection over a segment of the bone requires segmental resection to achieve complete debridement of all dead bone. In addition to these recommendations, segmental resection may be preferred when distraction osteogenesis is planned for the bone defect reconstruction.

Resection of the non-union followed by a two-stage procedure with the use of a spacer and bone graft/allograft, shortening, intercalary implant or bone transport after six weeks is unquestionably the gold standard of treatment [3–7]. Intravenous antibiotics are also very important in the treatment of infected non-united bone and can be used alone but functional blood supply is necessary for successful results [6,8]. A local muscle flap or pediculated bone graft with or without free flap can be used to gain infection control but these do not usually prevent infected bone resection [9–14].

In most cases, external fixation with Ilizarov´s method or unilateral fixators can be used successfully in combination with local application of antibiotic or bone-inducing agents [15–22]. Some authors describe the use of local cement application for several weeks before local bone grafting without segmental resection [23–27]. In some cases of septic non-union, the application of bone marrow with stem cells or human bone morphogenetic protein (hBMP) was used with good results [28–32]. Antibiotic-coated plates are also used in some cases [33,34]. In the ankle region specifically, arthrodesis can be an option to achieve septic union in infected cases by stabilizing the non-union site [35]and persistent drainage is only an option,albeit poor, in elderly patients [36]. It has been shown both in vitro and in vivo that cement coated implants or temporary cemented rods or spacers can be used without the need for segmental resection in septic non-union after nailing or with intramedullary infection [37–54]. There are indications where sufficient infection control for bone healing can be reached with stable implants.

Alternative strategies are the use of bioactive glass for osseous induction as an allograft or as carrier for antibiotics which showed promising results in infected bones – but blinded and randomized trials are still missing [6,55–61]. The loading of nano-particles with antibiotics, microspheres, polymer-lipids (and bacteriophages) is another very promising method, as is the induced membrane technique using beta-tricalcium phosphate [62]. The advantages of antibiotic release-control could be an important step in the treatment of infected bone non-union in the future, but Level I studies are missing here [63–81]. Furthermore, there are no comparative studies examining relative success of different debridement strategies.

Segmental resection is performed in cases of septic non-union with undersupplied, chronic infected and atrophic "dead" bone. In minor cases, segmental resection could be avoided by using other treatment options. Debridement strategies guided by Cierny's recommendations, including segmental resection when required, are recommended [82–85].

Eradication of infection is the main goal of the treatment and segmental resection can sometimes by the most useful method to accomplish this. Alternative treatments to segmental resection have not yet been determined to be as successful as the standard treatment. As of now, there is not enough evidence supporting a change of the accepted standard of care in septic non-union but some promising approaches are being explored.

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## QUESTION 8: What is the optimal management (Masquelet technique, bone transport) of postinfective bone defects in different long bones (tibia, femur, humerus, etc.)? How does this vary by type of defect (conical vs. cylindrical)?

**RECOMMENDATION:** The type of defect (cylindrical vs. conical) was not determined to be relevant to the treatment method. Instead, optimal management of partial vs. full segmental defects is relevant. Each long bone requires different preferred methods of stabilization.

**LEVEL OF EVIDENCE:** Moderate

**DELEGATE VOTE:** Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

### RATIONALE

The most complete systematic review was published in 2017 by Kadhim et al. [1] This review reported that in 96 femoral segmental bone defects, monolateral external fixation with bone transport was 99.7% effective for union and 94.7% successful for function compared with 88.9% and 57.6% for circular external fixation, respectively. Supplemental internal fixation in this study decreased the external fixation time. Yin et al. [2] reported their series of 38 femoral fractures with infected segmental bone defects (average size, 6.5 cm) that were treated with application of monolateral external fixation and bone transport. The mean external fixation index was 1.5 months/cm (range, 1.3–1.7 months/cm). Only five femurs required docking site bone grafting. Good/excellent results (evaluated using the Association for the Study and Application of the Methods of Ilizarov (ASAMI) Classification) for bone were 87.3% and good/excellent results for functional outcome were 79%. Multiple other studies have reported similar results with monolateral bone transport but with fewer numbers of patients [3–5]. Docking site bone grafting is not always necessary except in longer transports that result in fibrous tissue at the docking site with some atrophy of the transported bone end [4,5]. Monolateral bone transport is much less technically challenging than classic Ilizarov transport in the femur; therefore, this technique is more accessible to a larger number of surgeons.

Few studies document the success of vascularized fibular bone grafts (VFBGs) in post-infectious segmental bone defects [6–8]. Minami et al. [6] reported on 23 post-infectious femoral segmental bone defects treated with VFBG. Twenty of 23 patients achieved primary bone union; however, 2 patients had recurrent infections. Both of these patients underwent VFBG less than one month following resection for osteomyelitis; therefore, the authors' recommendation [6] was to delay the VFBG for longer than one month after the resection and until serologic infection markers returned to normal. Gao-Hong et al. [7] reported using VFBG for infected femoral segmental defects ranging from 6 to 18 cm with primary bone healing in 10 of 12 patients. Additional surgery improved the healing rate to 100% (12/12) with eradication of infection in all cases. According to Enneking scoring, excellent/good results were observed in 11 of 12 patients [7]. Han et al. [9] reported on VFBG for defects following infection with a primary union rate of only 48%. With additional procedures, this rate increased to 77% (46/60). The literature has small numbers of VFBG reconstruction for post-infectious defects of the femur with results that are not comparable to the success of bone transport. Song et al. [10] studied post-infectious femoral defects (> 8 cm) and compared 20 cases treated with internal bone transport to 17 cases treated with VFBG. The bone transport cases had 65% excellent/good result compared to 35% in the VFBG cases. The complication rate is high regarding donor site morbidity [11] and fibular stress fractures, which range between 15% and 32% [12,13]. The VFBG technique is technically demanding, requires microsurgical skills, and is not readily accessible to many orthopaedic surgeons.

No large series has been reported of the induced membrane technique for post-infectious defects of the femur. There are 3 series with 19, [14] 13, [15] and 13 cases [16]. Wu et al. [14] reported 19 cases with an average 5.5-cm defect (range, 2–10.9 cm). The first stage was external fixation and cement spacer placement. The second stage of treatment was combined internal fixation with autograft/auto-allograft mix into the induced membrane. All femurs united and were free of infection [14]. Yu et al. [15] reported 13 cases of septic femoral bone defects averaging 9.8 cm (range, 5–16 cm). The first stage fixation was an antibiotic-coated locked plate and the second stage fixation was an intramedullary nail. The reported union rate was 100%, and 92% of patients were infection free for at least one year [15]. Tong et al. [16] also reported 13 cases of femoral posttraumatic osteomyelitis. They compared bone transport to the induced membrane (IM) technique and found that the IM technique had better results in the