PART V

TRAUMA

Prevention

1.1. PREVENTION: HOST FACTORS

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QUESTION 1: What is the relationship between smoking and infection in fracture procedures? Is smoking history or only current smoking important? Does nicotine cessation at time of fracture reduce complication rates?

RECOMMENDATION: Smoking seems to increase the risk of infection in fracture procedures. The importance of smoking history versus current smoking status is unknown. It is also unknown if nicotine cessation (smoking) at time of fracture treatment reduces complication rates.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Smoking has been seen to have a negative effect in physiological and biological pathways. It interferes with the coagulation cascade (smokers clot faster), it impairs vascular function, and also interferes with the immune system (alters neutrophil function, migration and action) [1–5]. Even after smoking cessation, neutrophil phagocytic function continues to be impaired. Monocyte and macrophage correct function are key to prevent infection caused by *S. aureus* or *E. coli*, two of the most common infection-causing pathogens [3,4]. Smoking also affects the proliferative and remodelling phases of healing [6] by compromising epidermal regeneration and neovascularization and by causing decrease in perfusion and oxygenation [7,8].

The relationship between smoking and complications after fracture procedures has been widely studied [9,10]. Available literature suggests that smoking increases the overall incidence of complications including the risk for non-union and surgical site infection (SSI) [9–14]. Although the latter has not been consistent throughout studies, many authors continue to investigate this relationship.

Some available studies have not found smoking to be a definitive risk factor for infection [9–14]. One case control study that compared 140 smoking and 133 non-smoking patients with open tibia fractures suggested that infection might be multifactorial and not related to a single event [11]. A different prospective cohort study evaluating patients with limb-threatening open tibia fractures showed that current smokers were twice as likely to develop an infection compared to non-smokers (odds ratio (OR) 2.2; $p = 0.05$) [12]. That same study observed that previous smokers, compared to non-smokers, did not show any difference in terms of infection risk (OR 1.00; $p = 0.99$). Court-Brown et al. evaluated 178 patients who underwent fixation after calcaneal fractures [15]. They evaluated factors associated with infection including time to surgery, level of experience of the attending, smoking and type of wound closure. None of these were shown to be associated with infection. A randomized control trial allocated 105 smokers with a fracture requiring surgical treatment to a quit-smoking group ($n = 50$) or a non-quit-smoking group ($n = 55$) [16]. They found that the odds for presenting with a complication (superficial infection being the most common) was 2.51 times higher in the group that continued smoking compared to those who quit smoking, although this did not reach statistical significance. With similar findings, a recent systematic review found that there was no increased risk in smokers either for superficial or deep infection ($p = 0.13$ and $p = 0.33$, respectively) [14]. In terms of deep infection, retrospective studies have evaluated intramedullary nailing of tibia shaft fractures [17], open reduction and internal fixation (ORIF) of pilon fractures [18] and ORIF of acetabular fractures [19]. These concluded that there is no statistical significance related to smoking and increased infection rates. The most recent published study also showed that there was no statistically significant increased risk of infection in relation to smoking ($p = 0.45$) [20].

There is also evidence suggesting that smoking clearly increases the risk of infection in fracture procedures. Nasell et al. [13] evaluated 906 patients with ankle fractures that developed deep wound infections. They reported that these were more likely to be smokers than non-smokers (4.9% versus 0.8%; $p < 0.001$). They concluded that smoking was a risk factor associated with both deep and superficial wound infections (OR 6.0 and 1.7, respectively). Morris et al. [21] published a retrospective cohort study that included 302 bicondylar tibia plateau fractures treated with ORIF. Smoking was identified as the most important risk factor for deep infection (OR 2.40; $p = 0.02$). That same year Ovaska et al. [22] published a prospective cohort study that included 1,923 ankle surgeries with 131 deep surgical site infections. Smoking was shown to be statistically significant relative to infection in both the univariate (OR 4.0; $p = 0.004$) and multivariate analyses (OR 4.1; $p = 0.017$).

Two additional studies evaluated smoking-related complications in lower limb fractures. One consisted of a retrospective cohort study that included 519 patients with distal tibia fractures [23]. Smoking was associated with overall complications including infection (OR 3.40; $p = 0.039$). The second evaluated 30-day postoperative complications after ankle fracture fixation in a prospective cohort study [24]. They concluded that among the predictors for major local complications (deep wound infection and reoperation) peripheral vascular disease, open wound, contaminated wound classification and smoking (OR 2.85; $p = 0.0031$) were the strongest. Evidence from the last two years reveal smoking as an independent risk factor for

wound infection, as presented in a retrospective study managing 1,320 elbow fractures [25] and a case-control study from 318 calcaneal fractures [26]. In the first study, only smoking was found to have an association with infection after multivariate analysis (adjusted OR = 2.2; p = 0.023); the second study revealed that higher body mass index, delayed operation and active smoking (OR 19.497, p < .001) represented an increased risk for wound infection after ORIF.

Despite the conflicting evidence found in the literature, smoking seems to have a negative effect on overall complications and health and could potentially lead to an increased risk of infection. It is well-established that smoking has a detrimental effect on tissue healing and cellular pathways. Nonetheless, the current literature lacks the high-level evidence to state a direct relationship between these two factors. The recommendation provided here is inconclusive.

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QUESTION 2: What is the role of nutritional supplementation (NS) in avoiding infection in acute fracture cases?

RECOMMENDATION: (1) Evidence does not support the role of NS for avoiding infections in well-nourished individuals. (2) However, the literature has stated that in patients with a nutritional deficiency or catabolic state restoring nutritional parameters might reduce the risk of infection.

LEVEL OF EVIDENCE: (1) Limited, (2) Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Evidence in the available literature demonstrates that malnutrition is a significant clinical and public health problem. Several clinical trials present NS as a global effort in medicine, with applications in different specialties to improve the general condition of patients

with malnutrition or metabolic stress secondary to trauma or infection and to modulate the inflammatory response and potentially mitigate negative outcomes. Although there are controversial results, in spite of several studies with evidence level I on both supporting and refuting this initiative [1–7]. The literature has shown certain indications for prescription of NS in surgery, most recently defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline in 2017 [2]. There are two published meta-analyses concerning the effect of perioperative oral NS on elderly patients after hip surgery. The first combined 10 randomized control trials (RCTs) involving 986 elderly patients, which showed that oral NS had a positive effect on the serum total protein ($p < 0.00001$) and led to a significantly decreased number of complications ($p = 0.0005$). Furthermore, data from the infection subgroups showed significant decreases in wound infection (odds ratio (OR) = 0.17; 95% confidence interval (CI): 0.04, 0.79; $p = 0.02$), respiratory infection (OR = 0.26; 95% CI: 0.07, 0.94; $p = 0.04$), and urinary tract infection (OR = 0.22; 95% CI: 0.05, 0.90; $p = 0.03$) [6]. The second pooled the results from 11 RCTs (multinutrient, oral, nasogastric and intravenous supplementation), with an NS group of 370 elderly people controlled with a group of 357 elderly, non-NS patients. This study demonstrated a reduction in complication rates (e.g., pressure sores, chest infection) at 1-12 months in the NS group (123/370 versus 157/ 367; relative risk (RR) 0.71; 95% CI 0.59 to 0.86) [7], but not on rates of surgical site infection (SSI). However, NS use in an elderly population with acute fractures remains controversial and the prescription is reserved for underfed or malnourished patients in an attempt to reduce complications during hospitalization [2,6]. According to the World Health Organization (WHO) and ESPEN, malnutrition is considered when a patient has a 10-15% weight loss within six months, 5% in three months and/or has a Body Mass Index (BMI) under 18.5 kg/m^2. There are hematologic parameters evaluated throughout the literature, such as a serum albumin/globulin ratio below 1.5 (normal range), albumin below 3.0 g/dl, lymphocyte count below 1,500 cells/mm^3 and a lymphocyte//monocyte ratio below five versus one that allows selective screening of suspected malnutrition [3,5,8–10]. This is a special topic of interest in patients with factures, due to the fact that approximately 50% of patients with orthopaedic infections had some degree of malnutrition and immunosuppression regardless of age [3].

Evidence favoring NS has revealed that supplementation containing protein could produce beneficial effects by reducing the risk of infection in patients with fractures and nutrition deficiencies, regardless of age [2,4,5,11]. In a 2012 clinical trial, Myint et al. describe significant differences in BMI comparing the supplementation arm versus a control group [4]. Also, NS also prevents weight loss during a prolonged hospital stay, improving the general state of the muscles and muscular strength, which could reduce hospitalization periods and thus lead to shorter exposure to nosocomial microorganisms [7,12]. Long et al. reported that patients with poor nutritional status and with infections lose a higher amount of protein during postoperative states through urine [13]. Furthermore, an altered nutritional status reflects a depleted physiological state that affects humoral and/or cellular immunity, limiting an effective response to infection [3]. These findings might explain why early enteral administration of NS reduces the risk of septic shock with an active infectious process [12]. NS also seems to prevent long periods of delirium, which in turn is associated with an increased mortality rate [14].

Despite the previous evidence, there is also available literature against the use of NS [7,12,15]. For instance, NS administration near the time of surgical intervention does not seem to have an important effect, as it cannot effectively change the traditional nutritional markers such as albumin or transferrin [8]. However, in a 2012 clinical trial, Gunnarsson et al. reported evidence of the utility of monitoring the insulin-like growth-factor 1 to evaluate the response of nutritional support in the short term [9].

Some studies report that NS should be used with caution, considering metabolic phenomena such as refeeding syndrome, a condition associated with quick NS in patients with severe malnutrition. In this case, a sudden increase in insulin stimulates hypophosphatemia and produces a decrease in the extracellular adenosine triphosphate (ATP) and two to three diphosphoglycerate on erythrocytes producing arrhythmia, respiratory failure and hematologic alterations. Prevention, monitoring and adequate dosage are key to the success of preventing such complication [16–18]. Standard nutritional supplements containing arginine, omega-3 fatty acid, glutamine and other components (immunonutrition) have level I evidence supporting its use in avoiding infection after colorectal resection [1].

Another meta-analysis (eight RCTs and two observational studies) showed that multiple nutrient-enhanced formulas demonstrate a benefit in reducing the risk of SSI compared to standard NS (very low-quality evidence) [19]. The population studied included adult patients undergoing major surgical procedures (mainly cancer and cardiac patients). Orthopaedic surgical procedures, however, were not included in this meta-analysis.

In conclusion, these results suggest that NS can have positive effects on avoiding wound infection and other infectious complications (respiratory infection, urinary tract infection) only in elderly patients after hip surgery. There are several limitations in the current literature with respect to recommending NS in acute fractures for every patient. It would be necessary to conduct further research to investigate the role of immunonutrition in orthopaedics, especially with respect to fractures.

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QUESTION 3: Do preoperative pneumonia/urinary tract infections (UTIs)/trophic ulcers increase periprosthetic joint infection/surgical site infection (PJI/SSI) risk in femoral neck fracture patients treated by partial/total hip arthroplasty (THA)?

RECOMMENDATION: There is a paucity of literature examining whether pneumonia/UTI/trophic ulcers increase SSI/PJI risk for patients with femoral neck fractured treated by hemi- or THA.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Infection after femoral neck fracture treated with hemiarthroplasty/THA is an uncommon but devastating problem. The current literature cites a 1.7 to 7.3% risk of SSI after hemiarthroplasty for femoral neck fracture [1]. Commonly-cited risk factors for PJI/SSI after hemiarthroplasty for femoral neck fracture include higher Body Mass Index (BMI), prolonged surgery time, preoperative elevation in C-reactive protein (CRP) levels, surgeon experience level, reoperation and hematoma formation [2,3].

For patients undergoing primary total joint arthroplasty, pneumonia, UTIs and skin ulceration were shown to be predisposing factors for developing PJI [4–8]. However, there remains a lack of publications that specifically examine the risk of PJI/SSI related to the preoperative presence of pneumonia, UTI or skin ulceration in patients with femoral neck fracture treated with hemiarthroplasty or THA. One small prospective study demonstrated that UTI preoperatively was a significant risk factor for infection (odds ratio = 10; p = 0.04) [9]. A systematic review of the literature indicated that two or more urinary tract catheterizations during hospitalization was identified as a risk factor for SSI [1]. After a thorough investigation, we could not find any existing evidence of an association between preoperative pneumonia or trophic ulcers with the development of PJI/SSI after hemiarthroplasty or total hip replacement for femoral neck fractures.

In summary, there is scant or no evidence to suggest that preoperative pneumonia/UTI/trophic ulcers result in an increase in PJI/SSI risk in femoral neck fracture patients treated by partial/THA. The little evidence that is available is low quality and suggests that preoperative urinary tract infection increases the odds of PJI after hemiarthroplasty. Higher quality and larger scale studies are necessary in this subset population to make valid conclusions on this possible relationship.

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QUESTION 4: Are there microorganism-specific risk factors for acute infection in trauma patients (i.e., does being a nasal carrier of methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, increase the risk for MRSA infection after trauma?)

RECOMMENDATION: The current evidence of an increased risk of infection is based on several risk factors, including MRSA colonization, presence of external fixator, anatomical location of surgery and severe open fractures. In these situations, alterations in antibiotic prophylaxis could be considered.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

MRSA colonization in the nares, axilla and other body sites has been associated with higher risk for MRSA surgical site infection (SSI) (cardiac and arthroplasties) [1]. Nasal topical decolonization, along with systemic antibiotic prophylaxis, has been shown to reduce the risk of MRSA prosthetic joint infections (PJIs) [2]. In a meta-analysis published by Schweizer et al. a bundle intervention consisting of nasal decolonization and glycopeptide prophylaxis showed a significant protective effect against MRSA PJI and cardiac surgical infection when all patients underwent decolonization (0.40, 0.29 to 0.55) and when only *S. aureus* carriers underwent decolonization (0.36, 0.22 to 0.57). Because only three randomized clinical trials (RCTs) assessed the risk associated with total joint arthroplasty, they also included seven studies assessing nasal decolonization for general orthopaedic surgeries. Most of decolonization regimens used mupirocin ointment into the anterior nares. In addition, seven studies assessed the bundle applied only for patients colonized with MRSA and found a significant protective effect against SSIs with gram-positive bacteria (0.41, 0.30 to 0.56) [3]. Therefore, there is a strong recommendation to perform nasal decolonization for those patients known to be at high risk for MRSA PJI.

However, nasal colonization with MRSA as an independent risk factor for MRSA infection after orthopaedic trauma and fractures has yet to be investigated. Taormina el al. prospectively assessed whether trauma patients with fracture nonunions who are colonized with nasal *S. aureus* (MRSA or methicillin-susceptible *S. aureus* (MSSA)) would be at greater risk of complications following surgeries, and if it would predict positive operative cultures. The study failed to demonstrate an association between MRSA or MSSA-colonized patients being treated for fracture nonunion of long bones with postoperative infectious complications. There was no significant difference in operative culture positivity or speciation between colonized or non-colonized patients [4]. On the other hand, in recent a non-randomized, 7-year prospective study in Japan, Nakamura et al. examined the role of preoperative nasal swabbing for *S. aureus* among patients who underwent several types of orthopaedic surgeries. One hundred and forty patients were MRSA nasal carriers (carriage rate 3.4%), even though only a minority of them (40) underwent osteosynthesis for fracture stabilization [5]. Nasal carriage of *S. aureus* or MRSA developed significantly more SSIs compared to non-carriers, suggesting that it may be a risk factor for SSI in orthopaedic surgery. Additionally, Croft at al. prospectively screened for MRSA colonization in 355 patients admitted to a trauma intensive care unit, of which 36 (10.1%) were colonized. Significantly higher rates of MRSA infection were diagnosed in the MRSA colonized group (33.3%) compared to those who were not (6.6%) ($p < 0.001$). Death rates were also higher among the colonized group compared to non-colonized patients, (22.2 vs. 5.% [$p < 0.001$]). Therefore, they recommended MRSA screening protocols at trauma units to identify these at-risk patients [6].

The current evidence that MRSA colonization predicts acute infection in trauma patients is scarce, but it suggests that assessment and decolonization may be beneficial in reducing fracture-fixation infection rates. Nixon et al. screened 1,122 trauma patients, of whom 3.8% were MRSA carriers, and after implementation of anti-MRSA policies the incidence of MRSA infection dropped by 56% [7]. The same group, in a retrospective study, identified 3.2% (79/2,473) MRSA carriage at admission in an acute trauma unit, and these patients were significantly more likely to develop MRSA SSI (7 of 79 patients, 8.8%) compared with 54/2,394 (2.3%) of MRSA-negative patients ($p < 0.001$). This difference was confirmed on multivariate analysis, in which the odds ratio for developing MRSA SSI among MRSA carriers was 2.5 ($p = 0.015$) [8].

Conversely, Kan et al. analyzed 66 patients with femoral neck fractures and rates of MRSA colonization and found no correlation between MRSA colonization and higher rates of postoperative infection. Nevertheless, this study presented several important limitations including the postoperative infection evaluation limited to the first immediate postoperative week and short follow-up evaluation no longer than four months [9].

Older patients with femoral neck fractures seem to be particularly prone to be colonized by MRSA. A large French retrospective multicenter cohort study identified an SSI rate of 5.6% in patients who had surgery for a proximal femur fracture, of which one-third involved MRSA. All infected patients received first-generation or second-generation cephalosporin for prophylaxis, whereas those who received antibiotics effective against MRSA (i.e., vancomycin or gentamicin) for prophylaxis had no MRSA SSI [10]. Similarly, a prospective cohort study assessed the MRSA colonization rates among patients with proximal femur fracture in a German trauma unit. Their conclusion and recommendation is to systematically search for MRSA colonization in patients presenting with known risk factors by swabbing them in the emergency room [11].

The role of MRSA carriage eradication among trauma patients admitted to the intensive care unit (ICU) as an independent measure to prevent MRSA infection was assessed in a large multi-center, patient-based RCT recently published by Maxwell et al. Those with positive nasal swabs were randomized to either daily chlorhexidine gluconate (CHG) baths and mupirocin (MUP) ointment to the nares or soap and water baths and placebo ointment (S + P) for five days. Upon admission, 13.3% (90/678) of patients were MRSA carriers, and clinical MRSA infection was significantly more often diagnosed in MRSA colonized patients (21.1%) than those who were not (5.4%, $p < 0.001$). Although underpowered to draw definitive conclusions regarding the role of MRSA decolonization with CHG + MUP to

reduce MRSA infection rates, due to the smaller number of recruited patients per treatment arm, the five-day treatment period resulted in only a trend towards the reduction of colonization, 13 (59.1%) vs. 9 (90%) for CHG + MUP vs. S + P (p = 0.114). There was no difference in the proportion of MRSA infections between CHG + MUP (seven [31.8%]) vs. S + P (six [60%], p = 0.244). CHG + MUP was ineffective in eradicating MRSA from the anterior nares, but may reduce the incidence of infection [12].

A pilot RCT evaluated SSI among patients with open fractures that received prophylaxis during 24 hours with cefazolin compared with vancomycin and cefazolin, depending upon their *S. aureus* colonization status. MSSA and MRSA carriers were 20% and 3%, respectively. Although underpowered with a sample size too small for a clinical efficacy analysis, no significant difference in the rates of SSI was observed between the treatment arms. A significantly higher rate of MRSA SSIs was observed among MRSA carriers compared with noncarriers (33% vs. 1%, respectively, p = 0.003) [13]. Other factors that raise the risk of MRSA infection include the use of external fixation and a prolonged time to intramedullary nailing of long bone fractures [14].

Torbert's retrospective study identified *S. aureus* and gram-negative rods (GNRs) as most commonly seen in deep postoperative infections. GNRs were seen more frequently in the pelvis acetabulum and proximal femur injuries even in closed fractures. Resistance to GNRs was lower than *S. aureus,* and the infection rates for combined surgical approaches were twice that of a single approach for acetabular or pelvic surgery [15].

Severity of open fracture plays a role in the choice of antibiotics. There was no statistically significant difference in infection rates between the group treated with ciprofloxacin and that treated with cefamandole/gentamicin for Types I and II open fracture wounds. A high failure rate for the ciprofloxacin only treated Type III open fracture group, with patients being 5.33 times more likely to become infected than those in the combination therapy group [16].

The anatomic location of surgery should be considered when administering preoperative antibiotics. Corynebacterium genera are frequently associated with implants when surgical incisions were made near the perineum [17]. *Cutibacterium acnes* is bacterial species that is often seen in the axilla and coverage for these organisms should be considered when operating near this anatomical location [18].

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QUESTION 5: Is periprosthetic fracture a risk for the development of a periprosthetic joint infection (PJI)?

RECOMMENDATION: Infection rates from level III and IV evidence studies suggest an increased surgical site infection in patients who undergo re-operation for treatment of periprosthetic fracture of the femur after total hip and knee arthroplasty. There is limited literature available on periprosthetic acetabular and tibial fractures. Further study investigating the outcomes for treatment of periprosthetic fracture is recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic fracture about a hip or knee replacement can be a devastating complication. Almost all studies involving periprosthetic fractures are limited to small, retrospective case series and many of the studies focus on one type of treatment for one type of fracture. Additionally, most of these studies focus on the return to function and union of the fracture as primary endpoints. As a result, there is limited data on the risk of surgical site infection in the presence of a periprosthetic fracture.

Periprosthetic fractures about the acetabular component of a total hip replacement are uncommon and typically involve high-energy injuries. Treatment is based on the fracture pattern and stability of the implant. Protected weightbearing or revision surgery, often with supplemental fixation, are utilized for treatment. A retrospective review of 11 patients did not discuss infection as a complication [1].

Periprosthetic fractures about the femoral component of a total hip replacement are most commonly reported in the literature. These fractures can be treated either nonoperatively or surgically, based on the fracture pattern and stability of the implant. Plate fixation, revision hip arthroplasty or combination treatment are the most common methods of surgical treatment. A study from the Swedish joint replacement registry identified 1,049 periprosthetic femur fractures treated surgically over a 21-year period. Over this period, 245 patients underwent re-operation, the most common reasons for failure being loosening, re-fracture and non-union. There was an infection rate of 2.3% (24 cases), and infection was more common in the plate fixation group than the revision hip arthroplasty group [2].

A study from the Mayo Clinic demonstrated 5 (4.2%) deep periprosthetic infections after femoral component revision of 118 Vancouver Type B periprosthetic fractures [3]. Similarly, a systematic review of 22 studies totaling 510 Vancouver Type B2 and B3 fractures demonstrated 13 (2.5%) surgical site infections [4]. In cases of extremely poor bone stock, a retrospective review demonstrated a 19% infection rate in 19 proximal femoral replacements [5].

Periprosthetic fractures about the distal femur after total knee replacement can be treated nonoperatively or surgically based on the fracture pattern and stability of the implant. Fractures can be treated with intra-medullary nail fixation, plate fixation or revision knee arthroplasty. A systematic review of 415 fractures from 29 case series demonstrated an infection rate of 3% [6].

Periprosthetic fractures about the tibia after total knee replacement are rare (0.4 to 1.7%) and can often be treated nonoperatively [7,8]. Surgical treatment with plate fixation, intramedullary nail fixation or revision arthroplasty is uncommon, and the current literature is limited to small retrospective case series.

While randomization would be difficult due to limited previous experience with these complicated cases, future study should involve prospective, multi-centered investigations involving larger numbers of patients to gain a better understanding of the natural history and outcomes of patients who undergo treatment for periprosthetic fractures.

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QUESTION 6: Are there predictors of the need for allogeneic blood transfusion (ABT) in patients undergoing arthroplasty for acute hip fractures?

RECOMMENDATION: Preoperative predictors for the need for ABT include (1) anemia and (2) dementia and hypoalbuminemia. (3) Anticoagulation or anti-platelet medications do not predict the need for ABT. There is conflicting data with regard to the need for ABT when comparing hemiarthroplasty (HA) to total hip arthroplasty (THA).

LEVEL OF EVIDENCE: (1) Strong, (2) Limited, (3) Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Preoperative anemia is a known risk factor for ABT in patients undergoing hip and knee arthroplasty [1,2]. A retrospective study of 1,484 patients with hip fractures from 2007 to 2010 identified the risk factors for ABT as older age, lower hemoglobin on admission, female gender, type of surgical implant used (cephalomedullary nail and dynamic hip screw more than HA) and a shorter time from admission to surgery. The study is limited by transfusion thresholds, which may artificially increase the rate of ABT [3]. In hip fracture patients, regardless of fixation or fracture type, hypoalbuminemia [4] and dementia [5] are associated with an increased need for ABT.

Patients on chronic anticoagulation therapy are thought to be at risk for perioperative complications associated with bleeding. A level III retrospective study matched 62 patients with proximal femur fractures on warfarin with 62 patients not on anticoagulation therapy treated with an intramedullary nail, HA or THA. There was no significant difference in the rates of ABT in patients with international normalized ratio (INR) < 1.5 or with subgroup analysis of patients with an INR > 1.5 (range 1.5 to 3.1) [6]. There are three retrospective studies evaluating the preoperative use of clopidogrel in hip fracture patients with matched control patients comparing blood transfusion rates that report no significant increase in ABT [7–9].

A systematic review and meta-analysis of studies comparing surgical approaches and four studies comparing surgical approach for HA showed no difference in ABT rates between anterior, lateral and posterior approaches [10–13].

Perioperatively, medications such as hemocoagulase agkistrodon and tranexamic acid are administered to decrease blood loss. Multiple studies in the setting of femoral neck fracture have demonstrated a lower rate of ABT using these medications, but there remains a concern for increased risk of venous thromboembolism [14–17].

Much debate has centered on the treatment for displaced femoral neck fractures. Three prospective randomized controlled trials demonstrate no significant difference in the rate of ABT between cemented versus cementless femoral fixation in HA [18–20]. Multiple studies have reviewed differences between HA and THA for femoral neck fracture. Findings include longer operating times and increased blood loss in THA, but these studies can be difficult to interpret as patients undergoing THA are often younger and healthier [21,22]. Studies have demonstrated no difference in the rate of ABT [22,23], and increased rate of ABT in THA [21,24].

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1.2. PREVENTION: RISK MITIGATION

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QUESTION 1: Is there a role for bacterial decolonization (i.e., of methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, in nares) in trauma cases?

RECOMMENDATION: It is unknown if bacterial decolonization in trauma patients reduces surgical site infection (SSI).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

S. aureus colonization has been described since the early 1930s, and is linked to postoperative SSI in different surgical specialties, including orthopaedics. *S. aureus* resides in the nares, throat and skin surfaces in up to 30% of the population [1]. Establishing an association between bacterial carrier status and SSI in the setting of orthopaedic trauma has been challenging. The reported rate of MRSA carriers ranges from 1.8% up to 30% of hip and femur fracture patients [2–11], whereas the reported rates of MRSA-related SSI in those carrier populations ranges from 8.8% to 14.2% [6,12]. Furthermore, MRSA carriers displayed a higher incidence of other nosocomial infections and one-year mortality [4].

Although several published studies do support a connection between preoperative carrier status (for MRSA) with postoperative SSI development [13], it is uncertain whether it is due to the carrier status alone or due to other patient and disease factors [14]. One study refuted the need for widespread MRSA screening and eradication [15]. On the other hand, most literature has advocated addressing high-risk populations [6,9,16–18] for carrier status with prophylactic antibiotics against MRSA rather than decolonization preoperatively. Two main reasons have been postulated. First, one study found that in 86% of trauma cases in the setting of emergency fracture management, the results of MRSA screening would not be available before the surgical procedure commences [2]. Second, successful decolonization process will delay surgical procedures, which may not be ideal especially in hip fractures and open fractures.

With regard to decolonization, MRSA-related SSI was significantly reduced after decolonization protocol (without any reference to carrier status) from 2.3% to 0.33% [19]. However, one study demonstrated that MRSA screening and treatment policy reduced infection rates from 1.57% to 0.69% [5]. Furthermore, decolonization has been found to decrease total numbers of wound infection rather than wound infections caused by *S. aureus* [20].

For orthopaedic trauma cases, no prospective study of bacterial decolonization exists. The introduction of MRSA screening policies was evaluated in two retrospective studies including trauma patients [5,21]. Mupirocin was used for MRSA-positive patients, and both studies showed a significant reduction of postoperative MRSA infections. In a recent study on patients with lower extremity fractures, the addition of a povidone-iodine nasal swab in addition to a chlorhexidine-gluconate bath was evaluated [22]. Compared to two years before the start of the povidone-iodine intervention, the rate of SSI declined significantly.

Literature supporting decolonization in orthopaedic trauma patients only consists of low to moderate quality level 3 and 4 studies [19,20]. Literature not supporting decolonization consisted of one moderate quality level 1 study [23] and one low quality level 4 study [7]. As a result, a recommendation could not be made in favor of or against bacterial decolonization. Most importantly, screening should not delay surgical intervention in these patients, and these should be individually evaluated in a case by case scenario.

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Authors: Robert O'Toole, Nathan O'Hara

QUESTION 2: What are the ideal strategies to prevent secondary and nosocomial contamination of open fracture wounds which are left open?

RECOMMENDATION: Data support local antibiotics and early wound closure to reduce contamination of open facture wounds.

NOTE: The recommendation above was changed from the original version so the rationale below does not completely align with this recommendation. Please see Section 3:2, Question 2 for rationale for early wound closure. The rationale below regarding negative pressure wound therapy (NPWT) applies to Section 3:2, Question 4.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

METHODS

Randomized controlled trials, nonrandomized trials, prospective and retrospective observational studies were eligible for inclusion. We searched Medline, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to March 2018 for published studies without language restriction. Our search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) there was a comparison between patients treated with a secondary infection prevention strategy and a control group or a comparison between two or more secondary infection prevention strategies.

RATIONALE

Some high-grade open fractures are left open and return to the operating room for one or more repeat debridement surgeries. Traditionally the wound was packed with a gauze dressing, which was changed between surgeries. There is interest in using different strategies to decrease surgical site infection (SSI), which is often thought to be caused by nosocomial pathogens. The two main current treatment strategies are the use of the NPWT (wound VAC) or antibiotic bead pouches.

A systematic review of the literature reveals four randomized trials with conflicting results investigating the practice of NPWT over simple gauze dressings between surgical debridement, and there are no randomized trials examining the efficacy of antibiotic bead pouches.

Until recently, the literature investigating the use of NPWT tended to show a reduction in infection rates with its use. However, this conclusion was contradicted recently by the WOLFF trial [1] which is a well-powered (n = 460) prospective trial on open fractures requiring multiple debridements. Patients were randomized to either standard dressings or NPWT. No effect on SSI was shown (7% in negative pressure vs. 8% in standard dressing, p = 0.64) [2].

Prior to the publication of the WOLFF trial, the literature had consistently favored NPWT but in smaller or lower-quality studies as summarized in a recently-published systematic review of the literature [3]. Three of the papers included in the review assessed the effect of NPWT on reducing SSI in open fractures [4–6]. There have been two additional randomized trials published more recently [7,8] and we identified two other retrospective studies on this topic [2,9]. Two of the three prior randomized trials demonstrated reduction in infection with NPWT (28% vs. 5%, p = 0.02, n = 62 [4] and 11% vs. 5%, p < 0.05, n = 93 [7]) and the third (n = 90) had a very low event rate and revealed no difference [8]. Three more retrospective studies showed similar results with relatively large reductions in infection rates with NPWT (55% vs. 19%, p = 0.04 [8], 21% vs. 8%, p = 0.01 [3], 33% vs. 10%, p = 0.03 [2]), and a fourth identified no difference despite a potential selection bias against NPWT due to higher-risk cases in that group [8].

Despite the widespread use of this technique in North America, there are few studies investigating the use of local antibiotic beads. These are composed of polymethal methacrylate (PMMA) cement mixed with antibiotics placed into the wound in a "bead pouch" that seals off the wound between debridement surgeries. One small pilot randomized trial investigated IV antibiotics versus antibiotic beads without intravenous (IV) antibiotics and found no difference in infection rates [10]. Three similar retrospective studies by one group [11–13] should probably be considered as one study, as all the

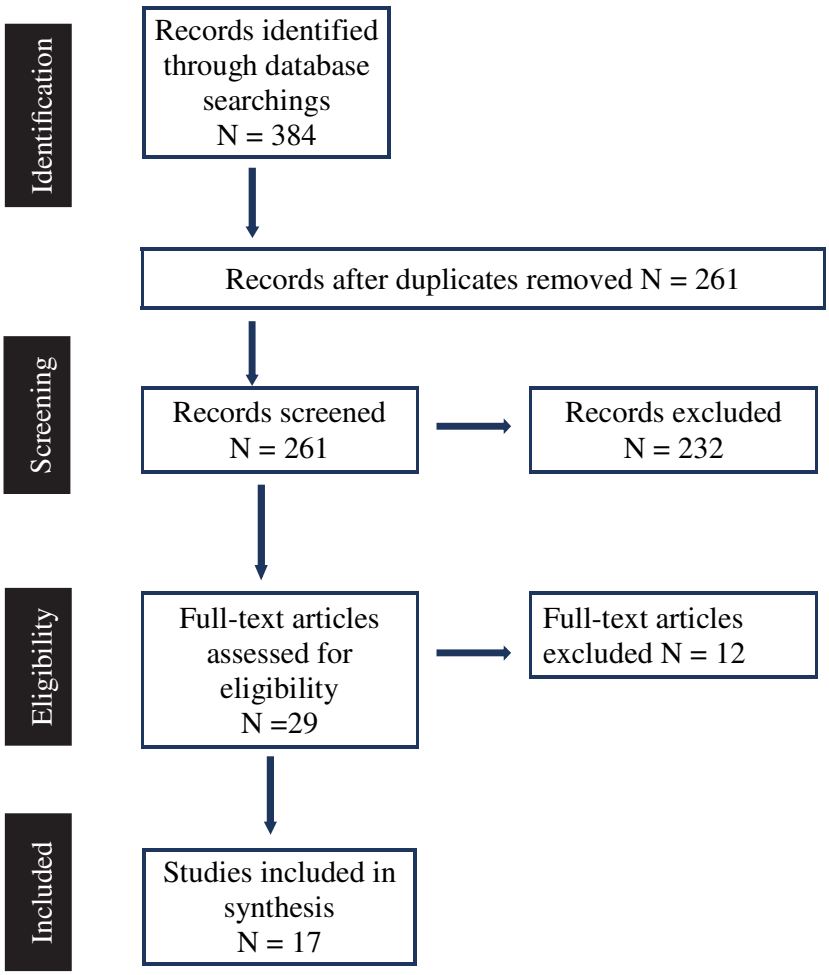

FIGURE 1. Flow diagram of study selection.

patients in one study appear to be included in the later study. This work demonstrated a significant reduction of infection rates (12% vs. 3.7%, p = 0.001) [12].

This said, one of the most important preventive measures seems to be the actual use of local antibiotics. A recent meta-analysis by Morgenstern et al., not included in this research strategy, suggests a risk reduction in infection of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. Most studies in this review used PMMA beads as local carrier for the antibiotics [14]. Furthermore, support for the use of topical antibiotics in open wounds is from recent animal studies in rats [15–17] and goats [18] by a single research group using contaminated open fracture models.

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APPENDIX – SEARCH STRATEGY (NO PUBLICATION DATE LIMIT)

Ovid Medline – 120 references retrieved on 03/22/2018
((open adj3 fracture*).ab,ti. OR "Fractures, Open".sh.) **AND**
((infection* or sepsis OR contamination).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.) **AND**
((beads OR "bead chains" OR "vacuum assisted closure" OR VAC OR "vacuum sealing" OR gel).ab,ti. OR "Negative-Pressure Wound Therapy".sh.)

Embase – 215 references retrieved on 03/22/2018
((open NEXT/3 fracture*):ab,ti OR 'open fracture'/de) **AND**
(infection*:ab,ti OR sepsis:ab,ti OR contamination:ab,ti OR 'infection'/exp OR 'wound infection'/de OR 'cross infection'/de OR 'hospital infection'/de OR 'sepsis'/exp) **AND**
(beads:ab,ti OR "bead chains":ab,ti OR "vacuum assisted closure":de,ab,ti OR VAC:ab,ti OR "vacuum sealing":ab,ti OR gel:ab,ti)
CINAHL – 35 references retrieved on 03/22/2018
((open W3 fracture*) OR MH Fractures, Open) **AND**
(infection* OR sepsis OR contamination) **AND**
(beads OR bead chains OR vacuum assisted closure OR VAC OR vacuum sealing OR MH "Negative Pressure Wound Therapy")

CENTRAL – 14 references retrieved on 03/22/2018 – in Title, Abstract, Keywords
(open NEAR/3 fracture*) **AND**
(infection* OR sepsis OR contamination) **AND**
(beads OR "bead chains" OR "vacuum assisted closure" OR VAC OR "vacuum sealing" OR gel)

Authors: Mitch Harris, Sofiene Kallel, Abhiram R. Bhashyam, Andre Shaffer

QUESTION 3: Is there a difference in the risk of periprosthetic joint infection (PJI) with use of internal versus external fixation for treatment of periprosthetic fractures?

RECOMMENDATION: Unknown. There is limited evidence comparing the risk of PJI with use of internal versus external fixation to treat periprosthetic fracture. The potential for pin tract infection, particularly with inadvertently placed intra-articular pins, make internal fixation the preferable treatment option in most cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The majority of studies that have explored this question describe periprosthetic femur fractures after total knee arthroplasty (TKA). Periprosthetic femur fractures following TKA are an uncommon complication (0.3 to 2.5% incidence rate per year), but are occurring more frequently given the higher rate of primary TKA and increased activity of the elderly patients who are at the highest risk [1–3]. Treatment options currently include nonoperative management (protected weightbearing, bracing, casting), open reduction internal fixation (ORIF), or, rarely, external fixation [1,4]. Given the success of ORIF, there are few reports on the use of external fixation [1,2,4]. In addition, external fixation has historically been avoided given the belief that external fixation pins near a total joint increases the risk for superficial and deep infection [2].

Within this specific clinical setting, there is limited knowledge given the lack of large series of periprosthetic femur fractures treated with either internal or external fixation. The only reports of external fixation for these fractures are case reports. Based on the current literature, there is no difference in the rate of deep infection following internal fixation (rate = 4%) versus external fixation (rate = 7%, p = 0.8). This analysis is severely limited by the small sample size, so it is difficult to make any definitive statement regarding the differential risk for PJI after internal or external fixation of periprosthetic fractures.

ORIF is preferred given its high rates of union and low rates of infection (~ 3%) [1,2,4]. For patients who are too ill or are contra-indicated for ORIF, treatment options include nonoperative management or external fixation. While the infection rate for nonoperative treatment is predictably low (0 to 1%), 31% of patients had complications related to malunion or nonunion [2,3]. Given this poor outcome, some have turned to external fixation [3,5–9].

A recent systematic review found that the rate of deep infection/PJI following ORIF was 4.1% (10 out of 245 reported patients). Among all published reports using external fixation, the rate of superficial pin site infection was 28.6% (4 out of 14 reported patients) and the rate of deep infection/PJI was 7.1% (1 out of 14 reported patients) [3,5–9]. The rate of PJI between internal versus external fixation was not statistically significant (p = 0.8 by chi-square test). Based on this data, the risk of PJI is not statistically significantly different following internal or external fixation of periprosthetic femur fractures, but this analysis is severely limited by small sample size.

There are only two case series that report on use of external fixation to treat periprosthetic fractures. Assayag et al. successfully treated two periprosthetic tibia fractures using a circular external fixation frame without superficial or deep infection [10]. Interestingly, Sakai et al. successfully treated an infected periprosthetic total hip arthroplasty femoral fracture with Ilizarov external fixation with resolution of the infection [11].

There has been no systematic study of this topic. Thus, it is therefore challenging to make a definitive statement regarding any possible differential risk for PJI after internal or external fixation of periprosthetic fractures. Internal fixation appears to be the preferable treatment method with a trend toward lower risk of PJI, as well as the potential for improved alignment and function with better reduction and fixation.

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APPENDIX - SEARCH STRATEGY

Databases: OVID-Medline, Google Scholar, Scopus

1. "Periprosthetic Fractures"[MeSH] AND "Infection"[MeSH]) AND ("external fixation" or "internal fixation")
2. "infection" and "periprosthetic fracture" and ("internal fixation" vs. "external fixation")
3. "infection" and "periprosthetic hip fracture" and ("external fixation") - Nothing
4. "periprosthetic tibia fracture" and "external fixation" – 1
5. "periprosthetic femur fracture" and "external fixation" – 1

COMBINED ANALYSIS

Paper	N	Superficial Infection	Deep Infection
Beris	3	2	0
Figgie	1	1	1
Biswas	5	0	0
Merkel	3	0	0
Simon	1	1	0
Hurson	1	0	0
Summary	**14**	**4 (28.6%)**	**1 (7.1%)**

($p = 0.8$; chi square result compared to results following ORIF)

Author: Maria Fernanda García

QUESTION 4: Should definitive fixation of fracture in a polytrauma patient and open abdomen be delayed until the abdomen is closed?

RECOMMENDATION: Definitive fracture fixation in the presence of an open abdomen should not be delayed and could be performed safely if the patient is suitable to undergo surgery.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Laparotomy is a well-established intervention in a polytrauma patient aimed to achieve rapid hemostasis and limit the contamination generated by intestinal, biliary or urinary leak [1–3]. However, abdomen closure cannot be carried out until edema has resolved to allow tension-free closure [1]. It is known that delayed abdominal closure after damage-control laparotomy reduces mortality, complications and length of stay. Nonetheless, definitive abdominal closure is not performed until the requirement for on-going resuscitation have ceased, no concerns regarding intestinal viability persist and no further surgical re-exploration is required [4]. Abdominal closure has been associated with fewer complications if performed within the the 4 to 7 days following laparotomy [4].

Early appropriate care of spine, pelvic ring, acetabulum and unstable femoral fractures in polytrauma patients decreases intensive care unit (ICU) length of stay from 9.4 to 4.5 days and total

hospital stay from 15.3 to 9.4 days [5]. However, definitive fracture fixation in patients with an open abdomen is often delayed due to the perceived increased risk of complications, specifically surgical site infection (SSI) [6].

One retrospective study has evaluated the safety of definitive fracture fixation in the presence of an open abdomen [6]. This study supports early definitive surgical management of spine, pelvic, acetabular and long bone fractures through minimally invasive techniques and standard open approaches. Time from injury to fixation surgery averaged 4.4 days when it was done in the presence of an open abdomen and 11.8 days when it was deferred until abdominal wall closure. The incidence of SSI that required surgical intervention was 3.1% in the first group and 30.6% in the second. No significant differences were found in terms of mortality, hospital length of stay or number of ventilator-dependent days.

Based on the limited available literature, there is no reason to delay definite fracture fixation in polytrauma patients with an open abdomen. Patients may benefit from early fracture fixation, not only from having reduced ICU and overall length of stay reduction, but infection risk reduction as well. We recommend that patients undergo definitive fracture fixation in the setting of an open abdomen if the patient is medically stable, does not have an active infection and is suitable to undergo surgery.

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Diagnosis

Authors: Andres Pinzon, Kenneth Egol

QUESTION 1: Which open fracture classification system currently used (Gustilo-Anderson classification or the Orthopaedic Trauma Association's open fracture classification (OTA-OFC)) is preferred, based on interobserver reproducibility and predictiveness of outcomes?

RECOMMENDATION: OTA-OFC is preferred. Based on currently-available data, the OTA-OFC provides a more robust description of the injury with interobserver agreement that is comparable or superior to the Gustilo-Anderson classification. Additionally, the OTA-OFC, according to its subcategories, may predict outcomes such as the likelihood of early amputation and need for adjuvant treatments.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The Gustilo-Anderson classification was introduced in 1976 for use in describing open fractures of the tibia [1,2]. Originally comprised of Types I through III, Type III was later subdivided into subtypes A through C to allow for the classification of "severe" fractures with greater specificity [2,3]. It has since been adopted for describing open fractures of all long bones and remains the most widely-used system for classifying open fractures [2].

The Gustilo-Anderson classification was found to have only moderate interobserver agreement when investigated by Horn et al. [4] and Brumbeck et al. [5], with an overall agreement of 66% and 60%, respectively. Clinically, the Gustilo-Anderson classification is well-established as a predictor of infection and amputation [1–3,6–8]. It provides a method of stratifying open fractures broadly into "mild" and "severe" categories.

The OTA-OFC was introduced in 2010 as a system for describing open fractures of all locations [9]. Rather than utilizing a single composite score, the OTA-OFC is comprised of five discrete components (skin, muscle, arterial, contamination and bone loss) each of which are independently rated mild, moderate or severe [9].

Studies suggest that inter-observer agreement throughout the OTA-OFC system is "moderate" to "good" overall [10,11], a statistic that is comparable or superior to that which has been reported for the Gustilo-Anderson classification [4,5,10]. This must be interpreted with caution, however, as the OTA-OFC is not aggregated and inter-observer agreement is not comparable among the five categories [10]. Studies assessing reliability have found that agreement is less robust within the muscle, bone loss, and contamination categories of OTA-OFC, suggesting that these categories may benefit from revision or clarification [10,11].

Initial studies in predictive utility of the OTA-OFC are promising. Agel et al. found different categories useful in predicting certain treatment modalities: the skin category for vacuum-assisted closure; bone loss category for antibiotic bead placement; skin and muscle categories for multiple debridements; and skin, contamination and arterial injury categories for early amputation [12]. Johnson et al. found it to be predictive of amputation and infection within 90 days [13]. Hao et al. found it to be predictive of amputation when the cumulative score was ≥ 10 [14].

While further studies validating the OTA-OFC are needed, the current literature suggests that it provides a method of describing open fractures with greater specificity compared to the Gustilo-Anderson classification with comparable inter-observer agreement.

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QUESTION 2: What diagnostic criteria must be fulfilled to diagnose surgical site infection (SSI) or fracture related infection (FRI) in orthopaedic trauma (including external fixators)?

RECOMMENDATION: Diagnostic criteria proposed by the International Consensus Group on FRI (published in 2017) should be used to diagnose infection in fracture cases. In cases, more than four weeks from fracture, histological confirmation of > 5 neutrophils per high power field is confirmatory of infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 5%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Unlike periprosthetic joint infections (PJI) which have clearly-defined diagnostic criteria [1], infection associated with orthopaedic trauma procedures does not. Orthopaedic trauma has a higher rate of SSIs compared to other surgical specialties, yet it lacks an infection definition agreement [2–4]. This is likely due to the great variety and complexity of skeletal trauma and variability of surgical procedures. According to the initial Centers for Disease Control and Prevention (CDC) definition of SSI in trauma, this could occur up to one year following surgery [5]. However, in their last revision, this time period has been reduced to 90 days [6]. This poses a challenge for diagnosis, since infections related to orthopaedic trauma are often subclinical and some only display pain without any other signs or symptoms [5,7]. Furthermore, the CDC guidelines distinguish between superficial incisional, deep incisional and organ/space infections. Bonnevialle et al. already stated that the term "superficial infection" is at best arbitrary [8], and poses particularly challenging problems in infection associated with orthopaedic trauma. Finally, in orthopaedic trauma research, these terms (e.g., superficial and deep) are often used inaccurately or inappropriately, which makes comparison of literature difficult [9]. In the current clinical literature, numerous terms other than SSI are used with respect to infections associated with orthopedic trauma procedures (e.g., posttraumatic osteomyelitis, osteitis). Often, no distinction is made between the terms osteitis and osteomyelitis. Overall, these terms seem not useful as the main issue is the presence of bacteria at the fracture site and around the implant, rather than the semantics of the pathogenesis of the infection [9].

Orthopaedic trauma surgeons realized that the definition for PJI, criteria for osteomyelitis and the CDC guidelines could not be easily extrapolated to fracture cases, and, therefore, a definition had to be developed. This was recently confirmed by an international survey for registered AOTrauma users. In this survey, surgeons were asked about the need for a working definition, and 90% of more than 2,000 surgeons who responded suggested that a definition solely focusing on infection in orthopaedic trauma (i.e., fractures) was required [10]. Therefore, a special effort was made, with the support of multipele orginazations, to develop (AO Foundation and European Bone and Joint Infection Society (EBJIS)) [9] and update (AO Foundation, Orthopaedic Trauma Association (OTA), EBJIS and PRO-Implant Foundation) [11] a consensus definition. The consensus group designated infection related to orthopaedic trauma (i.e., fractures) as FRIs and established a definition based on two different kinds of diagnostic criteria: confirmatory (infection definitely present if a confirmatory criterion is met) or suggestive (features associated with infection and requiring further investigation) criteria (Table 1).

Without question this consensus definition should be validated by prospective data collection in order to gather evidence of its use in clinical studies and to prove that it can become a valuable tool in comparative research.

TABLE 1. Criteria to define FRI

Confirmatory Criteria	Suggestive Criteria
1. Fistula, sinus or wound breakdown.	1. Clinical signs: pain increasing over time, local redness, local swelling, increased local temperature or fever.
2. Purulent drainage or presence of pus.	2. Radiological and nuclear imaging signs
3. Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens.	3. Pathogenic organism identified by culture from a single deep tissue/implant specimen.
4. Presence of more than five polymorphonuclear neutrophil per high power field, confirmed by histopathological examination [12].	4. Elevated serum inflammatory markers: ESR, WBC, CRP
	5. Persistent or increasing wound drainage.
	6. New-onset of joint effusion in fracture patients.

FRI, fracture-related infection; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell

External Fixation

The infection rates reported with the use of external fixators are higher than with osteosynthesis with an incidence of infection of up to 71% [13]. However, there is also no clarity in regards to the diagnosis of SSI in external fixation. There are two classification systems, Checketts-Otterburn and Sims, neither of which have been validated [13,14]. The most commonly used is the Checketts-Otterburn schema, which describes clinical signs such as redness, discharge, pain, edema, radiological changes in the screw-bone interface and compromise in several levels [15].

In conclusion, there is a scarcity of scientific evidence regarding diagnostic criteria to define SSIs in orthopaedic trauma. The CDC published guidelines for SSIs, which distinguish between superficial incisional, deep incisional and organ/space infections, seem not suitable to define/diagnose infection in orthopaedic trauma patients. The recently published, and thereafter updated, international consensus definition seems an adequate replacement. This definition introduces, instead of SSI, the term FRI. Furthermore, two levels of certainty around the diagnostic features are defined. Criteria can be confirmatory (infection definitely present if a confirmatory criterion is met) or suggestive. This definition should be validated by prospective data in the future.

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QUESTION 3: What diagnostic criteria define infected non-union of long bone?

RECOMMENDATION: The lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. The combination of the consensus definition of fracture-related infection (FRI) with a nonunion is a reasonable starting place, however definitions of nonunion vary and both the FRI definition and any proposed criteria for long bone nonunion will need scientific validation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Introduction

FRI is a feared musculoskeletal complication and one of the most challenging in trauma surgery. Currently, estimating the impact of FRI has been hampered by the lack of a clear definition [1,2]. Interestingly, this issue was previously raised in an Arbeitsgemeinschaft Osteosynthesefragen/Association for the Study of Internal Fixation (AO/ASIF) scientific supplement publication by Arens et al. in 1996, wherein the authors stated in a combined clinical and experimental study on FRI, "It is astonishing that in all papers in which infection is mentioned, the term 'infection' is not defined" [3]. In fact, this was confirmed by a recent systematic review, which showed that only a minority of randomized controlled trials (2%) in fracture cares use any kind of standardized definition of FRI [4]. The lack of a clear definition of FRI mirrors the situation for prosthetic joint infection (PJI) identified many years ago [1–5]. The situation for PJI [6] and diabetic foot infection, for example [7], has improved with consensus definitions emerging in recent years. Orthopaedic trauma surgeons realized that neither the definition for PJI nor the Centers for Disease Control and Prevention (CDC) guidelines could be easily extrapolated to fracture cases and that a definition for FRI had to be developed.

This was recently confirmed by an international survey for registered AOTrauma users. In this survey, surgeons were asked about the need for a working definition of FRI and 90% of more than

2,000 surgeons who responded suggested that a definition of FRI is required [8]. Therefore, a special effort was made, with the support of the AO Foundation, to develop such a consensus definition. The process that was followed was comparable to the one described by Cats-Baril et al. for the new definition on PJI [9]. Finally, in 2016, a consensus meeting concerning this topic was held with an international expert panel. This resulted in the current consensus definition for FRI, which was recently published [10]. This resulted in the current consensus definition for FRI, which was recently published and adopted by the AO Foundation and the European Bone and Joint Infection Society (EBJIS).

Classifications

There are multiple classifications described in the literature that subdivide FRI into discrete groupings, such as acute and chronic infections, or early, delayed and late-onset infections [2,11–13]. The authors of the recently-published consensus definition stated that there should only be a single definition for FRI based on specific diagnostic criteria. Two primary reasons were proposed for this decision. First, a subdivision would make such a definition unnecessarily complex and difficult to use in daily practice. Second, although the available classifications are time-related, these time windows are not based on scientific evidence. This supports the view that they are poorly-defined for FRI (e.g., time since injury, or time since onset of symptoms) and somewhat arbitrary. All these concerns pose serious problems from a definition point of view [4]. The authors did agree that acute and chronic infections are different entities that may require different treatment strategies, however it should not affect the way clinicians define FRI [10].

Diagnostic Criteria

Recent systematic reviews, of which two are currently under submission, have been performed to analyze the value of specific diagnostic criteria for FRI. Below, three systematic reviews on diagnostic criteria are summarized.

Clinical Criteria

Studies specifically focusing on clinical criteria to diagnose FRI are currently scarce and validation studies are nonexistent. In two systematic reviews, clinical criteria used to define FRI were described. In a study by Metsemakers et al., the aim was to identify definitions used in the literature to describe infectious complications after internal fixation of fractures [4]. A total of 100 randomized control trials (RCTs) were identified in the search. Clinical signs used to diagnose FRI in the included studies were: purulent drainage (16 studies), wound dehiscence/breakdown (5 studies), rubor (redness) (5 studies), calor (warmth) (4 studies), tumor (swelling) (4 studies), unspecified signs (4 studies) and fever (3 studies). Other parameters that were used to diagnose FRI were positive cultures (15 studies), treatment with oral antibiotics (6 studies), need for surgical debridement (5 studies), need for implant removal (4 studies), radiological signs (2 studies) and C-reactive protein (CRP) levels (1 study). Most authors included purulent drainage or discharge and positive cultures as parameters for the diagnosis of FRI [4].

In an ongoing systematic review by Bezstarosti et al., the authors are aiming to provide an overview of the available diagnostic criteria, classifications, treatment protocols and patient-related outcome measures for surgically treated FRIs between 1990 and 2017. Clinical signs used in the 93 included studies were: purulent drainage or discharge (34 studies), pain (14 studies), tumor (swelling) (9 studies), calor (warmth) (8 studies), wound dehiscence/breakdown (7 studies), rubor (redness) (7 studies), fever (5 studies) and unspecified signs (46 studies). It seems that swelling, pain and redness are often seen as signs of FRI, however, they are subject to interpretation and are difficult to measure. "Purulent drainage" and "wound dehiscence/breakdown" on the other hand, seem more appropriate as hard endpoints in the diagnosis of FRI.

Serum Inflammatory Markers

In an ongoing systematic review by van den Kieboom and Bosch et. al, the diagnostic value of the serum inflammatory markers CRP, leukocyte count (LC) and erythrocyte sedimentation rate (ESR) in suspected FRI were assessed. A total of 8,280 articles were identified, of which 6 [14–19] were included in this review. CRP, reported in 6 studies, appeared to be the most useful serum inflammatory marker with a sensitivity ranging between 60.0 and 100% and specificity between 34.3 and 85.7%, which is in line with current clinical practice [20]. LC was reported in five studies. Sensitivity ranged from 22.9 to 72.6% and specificity from 73.5 to 85.7%. Five studies investigated ESR; sensitivity and specificity ranged from 37.1 to 100% and 59.0 to 85.0% respectively. For the meta-analysis, four CRP studies, four LC studies and three ESR studies could be pooled. Meta-analysis of pooled results demonstrated only limited diagnostic value of the individual markers. Four studies analyzed the value of combining markers and reported an increased diagnostic accuracy. However, these results should be interpreted with caution as this is based on limited data from heterogeneous studies. Indeed, the results of all serum markers vary greatly between studies. Another issue identified when analyzing these studies was that different measuring devices, lab protocols and/or thresholds were used across studies. The authors, therefore, concluded that the analyzed serum inflammatory markers (CRP, LC and ESR) appear to be unsuitable to rule out or diagnose FRI. When these markers are used in a diagnostic flow chart, they should be interpreted with caution [10]. Future research protocols using continuous serum inflammatory marker values and standardized lab protocols are required to assess their combined value in the diagnosis of FRI.

Tissue and Sonication Fluid Sampling

In an ongoing systematic review, Onsea et al. analyzed the available evidence on sonication of fluid sampling and tissue tests for the diagnosis of FRI. Out of 2,624 studies, ten [14,21–29] fulfilled the predefined inclusion criteria. Five studies [21–25] focused on sonication fluid culture, two on polymerase chain reaction (PCR) [14,26] and two on histopathology [27,28]. One additional histopathology study [29] was found after screening of reference lists. The review demonstrated that there is evidence that sonication fluid culture may be a useful adjunct to conventional tissue culture, but there is no strong evidence that it is superior or can replace tissue culture. Regarding molecular techniques and histopathology, the evidence is even less clear. Overall, studies had variable gold standard definition criteria for comparison and poorly-reported culture methods. By updating the review, one additional paper [30] was found that is currently in press. In this study by Morgenstern et al., including unhealed FRI cases more than four weeks from the occurrence of the fracture, a bimodal cut-off for the presence of polymorphonuclears (PMNs) provided encouraging results in reducing the number of cases in which the diagnosis was uncertain [29]. During a recent second consensus meeting (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) it was decided that this cut-off for the presence of PMN's was included as a confirmatory sign for FRI.

Finally, in the systematic review by Onsea et al., the authors concluded it is imperative that lab protocols become standardized and that uniform diagnostic criteria, as recently published in a consensus definition, are implemented.

Imaging Modalities

In a recent systematic review by Govaert et al. [31], the recent literature (from 2000 to 2016) on imaging techniques for the diagnosis of post-traumatic osteomyelitis was analyzed. The literature search yielded 3,358 original records, of which 10 articles [32–41] were included. This review included seven studies on different nuclear imaging techniques, two studies on magnetic resonance imaging (MRI), one study on computed tomography (CT) with no studies identified regarding plain X-ray. The sensitivity for white blood cell (WBC) count or anti-granulocyte antibody (AGA) scintigraphy ranged between 50 and 100%, specificity ranged between 40 and 97%. For fluorodeoxyglucose positron emission tomography (FDG-PET), sensitivity and specificity ranged between 83 and 100% and between 51 and 100%, respectively.

WBC scintigraphy combined with hybrid imaging technique of single photon emission computed tomography combined with CT (SPECT/CT) was assessed by two studies. A higher diagnostic accuracy was reported in both studies that used this combination. Three studies investigated the combination of FDG-PET with PET-CT, which provided a significant increase in diagnostic accuracy. However, the studies that looked into these combinations provided only limited information. The authors concluded that, compared to other imaging techniques, either WBC or AGA scintigraphy combined with SPECT/CT and FDG-PET combined with CT demonstrates the highest diagnostic accuracy for the diagnosis of post-traumatic osteomyelitis when compared to other imaging techniques. It should, however, be taken into account that these results are based on a small number of studies and that imaging techniques and patient populations were heterogeneous across studies.

By updating the systematic review, two more studies from the past two years could be found. A study by Govaert et al. [42], aimed to establish the accuracy of 192 WBC scintigraphies for diagnosing FRIs, and investigate whether the duration of the time interval between surgery and WBC scintigraphy influences its accuracy. The authors concluded that WBC scintigraphy had a diagnostic accuracy of 92% for the detection of FRI in the peripheral skeleton. The duration of the interval between surgery and the WBC scintigraphy did not influence its diagnostic accuracy. The second study, by van Vliet et al. [43], evaluated the efficacy and diagnostic accuracy of a semi-quantitative measure, maximum standard uptake value (SUVmax), for the interpretation of FDG-PET/CT in the differentiation between aseptic and septic delayed union of the lower extremity. A total of 30 patients were included: 13 patients with aseptic delayed unions and 17 patients with septic delayed unions. Mean SUVmax in aseptic delayed union patients was 3.23 (SD ± 1.21). Mean SUVmax in septic delayed union patients was 4.77 (SD ± 1.87). A cut-off SUVmax set at 4.0 showed a diagnostic accuracy of 70% to differentiate between aseptic and septic delayed union. The authors concluded that the application of SUVmax for the interpretation of FDG-PET/CT imaging seems to be a promising tool for the discrimination between aseptic and septic delayed union. However, as this is based on a small number of patients, they acknowledge that larger, prospective trials are necessary to make a further statement regarding the role of FDG-PET/CT in the diagnosis of FRI.

Due to the current lack of high-quality evidence on the value of imaging techniques, which is similar to the other diagnostic criteria discussed above, imaging techniques seem not suitable to rule out or diagnose FRI and can only be considered a suggestive sign [10]. This was also included in the recently updated (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) international consensus definition of FRI.

The definition for non-union is currently not standardized, which makes it difficult to introduce diagnostic criteria for infected non-union. This said, overall there is little scientific evidence regarding the diagnostic criteria for FRI. With respect to serum inflammatory markers, tissue, sonication fluid sampling and imaging modalities, only a small number of studies are available. Validation studies on clinical parameters are nonexistent. This lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. Moreover, it seems that developing diagnostic criteria for *both* acute/early infections and chronic/late (e.g., infected nonunion) infections is arbitrary and complicates clinical decision-making. Finally, although the scientific evidence on diagnostic criteria to define FRI is scarce, the international Consensus definition of FRI that was recently updated seems an adequate start and offers clinicians the opportunity to standardize clinical reports and improve the quality of published literature. In our opinion, this definition should be validated by prospective data collection in the future.

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QUESTION 4: What differentiates acute from chronic osteomyelitis (OM)? Is it clinically important to distinguish one from the other?

RECOMMENDATION: Current literature is lacking consistent criteria for a distinct time point that differentiates the acute and chronic forms of infection. Differentiating between acute and chronic types may have practical implications on treatment plan and final prognosis.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

To address this question an extensive search of the literature was conducted. Our search aim was to identify articles reporting on the diagnostic criteria for acute or chronic osteomyelitis. A clear definition of OM in terms of temporal evolution was considered mandatory. Furthermore, in order to investigate the potential practical significance of the temporal distinction of OM into acute or chronic types, we aimed to identify papers reporting on the outcome of antimicrobial therapy or combined treatment (antimicrobial plus surgical intervention) of acute osteomyelitis. Our exclusion criteria included case reports, expert opinions, experimental studies, infections associated with prosthetic implants, diabetic ulcers and non-orthopaedic bone infections (facial, cranium, ribs).

We searched the Medline, Embase, Ovid, Cochrane and Google Scholar databases using the PubMed search engine. Our search strategy included the following Medical Subject Headings (MeSH) terms and Boolean operators: ("osteomyelitis"[MeSH Terms] OR

"osteomyelitis"[All Fields]) OR "bone infection"[All Fields] OR "osseous infection"[All Fields] AND ("classification"[Subheading] OR "classification"[All Fields] OR "classification"[MeSH Terms]). This search process yielded 856 records. After rejection of duplicates and irrelevant articles by their title or abstract, there remained 45 papers for which full text was obtained. After careful screening against the eligibility criteria, there were ultimately eight eligible articles left.

A second search process was run in parallel, as follows: acute [All Fields] AND ("osteomyelitis"[MeSH Terms] OR "osteomyelitis"[All Fields]) AND "humans"[MeSH Terms]. It yielded 3,339 results. After removal of duplicates and rejection of irrelevant articles based on their title or abstract, there were 56 studies remaining, for which a full text was obtained. Eventually, after screening of these manuscripts against the eligibility criteria, another 11 eligible articles were obtained. In addition, another 4 articles were added from handsearch of the relevant bibliographies, leading to a total of 23 eligible articles (see Fig. 1).

OM is an inflammation of the bone and bone marrow caused commonly by pyogenic bacteria, and rather infrequently by mycobacteria or fungi [1,2]. It is classically classified by the duration of its clinical course as acute or chronic. Acute osteomyelitis represents the early stage of the evolutionary process of the disease, usually characterized by an intense clinical picture. Its diagnosis is based on a combination of clinical, laboratory and imaging findings, with a definitive diagnosis established by positive bacterial cultures of aspirate, bone or blood samples [3]. A longstanding infection which progresses to bone necrosis and sequestrum formation is termed chronic OM [1,2,4]. This condition is usually characterized by more subtle clinical findings, occasionally the presence of draining sinus tracts, or may progress intermittently [5]. While the clinical differentiation is marked by necrosis and sequestrum formation, defining a specific time threshold beyond which an acute infection could be considered chronic is difficult [1,2]. The current literature is lacking consistent criteria for a distinct time point that differentiates the acute and chronic forms of infection. Nevertheless, this distinction is of only limited value in adults as they are very rarely affected by acute OM and, even if this does occur, prompt diagnosis before transition to chronicity is often missed. On the contrary, in children, who are frequently affected by acute hematogenous OM, differentiating between acute and chronic types has practical implications regarding the treatment plan and final prognosis. This is mainly due to the fact that younger patients have the ability to resorb, at least to some degree, devitalized bone tissue, thereby removing foci of "biofilm type" of bacterial growth and potentiating the effectiveness of early-instituted antimicrobial treatment [6]. Additionally, the duration of this antimicrobial treatment differs between acute and chronic OM, with the acute form being treated with three to six weeks of specific antimicrobials targeted at identified pathogens after initial empiric formulations, and the chronic form being treated for up to six months with targeted antimicrobial therapy without initial empiric therapy [7]. This is due to the fact that certain pathophysiological changes that occur during the evolution of the inflammatory process (such as pus formation, reparative reaction, formation of involucrum and bone sequestration), which dictate the treatment plan and prognosis, are time-dependent [8]. Consequently, the differentiation between an acute and chronic form, especially in children, has important implications on the treatment plan.

Some authors do not utilize strict temporal criteria for defining OM. In 1970, Waldvogel et al. emphasized the difficulty in distinguishing between acute and chronic OM in terms of clinical course (type and duration of symptoms) or histologic findings [9,10]. They classified all cases as either "initial episodes" or "recurrences." An initial episode was thought of as representing an acute type of the disease spectrum, while recurrences represented chronic cases. They documented significantly higher treatment failures in "recurrences" as compared to the "initial episodes" for both hematogenous cases ($p = 0.003$) and those secondary to a contiguous focus of infection ($p = 0.0005$). The same definition of acute OM as "initial episode" was adopted by Lieu et al. in a retrospective study of 95 patients aged less than 17 years [11]. Fifty-five percent of them had been treated conservatively, while the remaining 45% had received combined treatment (antimicrobial therapy plus surgery). A recurrence rate of only 8.5% was documented. Other authors utilized a list of clinical, laboratory and imaging criteria to define acute OM in children and adolescents [12–14].

Various temporal thresholds have been used to define acute OM (Fig. 1). The shortest time threshold was one week, and was documented in three studies reporting on pediatric populations (584 children) [15–18]. The percentage of surgical intervention across all three studies ranged from 5.3% to 56%, and the recurrence rate of the infection ranged from 0 to 12% (pooled estimate of effect size for recurrence rate [random effects model]: 3.5%, 95% confidence interval (CI): 0.1 to 11.5%, with significant statistical heterogeneity: $I^2 = 87\%$). In one study, a sub classification of acute hematogenous OM was proposed into early-acute OM (diagnosed within 48 hours of onset in children over one year of age), late-acute OM (diagnosed at 5 days or more in children over 1 year of age) and neonate-infantile type [16]. The rationale for this classification was based on the findings of the study that the success rate of antimicrobial treatment was 92% for early-acute type versus 25% for late-acute OM. Another commonly-used threshold was two weeks and was utilized by studies reporting on either pediatric [19–21], adult [22] or mixed populations [23]. Two out of the three studies dealing with the pediatric population reported on the recurrence of the acute infection, which ranged from 0 to 7% (pooled estimate of effect size [random effects model]: 3.6%, 95% CI: 0.02 to 13%, $I^2 = 79\%$), with the rate of operative intervention ranging from 8 to 44% [19,20]. Finally, in one study reporting on open, infected bone wounds of the distal fibula/tibia, an acute infection was considered when the duration of open wound drainage was less than six weeks [24].

The definition of chronic OM is much more variable in the literature. Various lower limits of duration of symptoms exist, above which a chronic osseous infection is considered (Figs. 2 and 3). These range from at least a week in one study [17] to at least six months in three studies [25–27]. In-between, there are studies using the lower limits of two weeks [23], six weeks [24], one month [22] and two months [28]. However, in all studies the most consistent sign of chronicity of infection was bone sequestration. In a recent systematic review of the literature on the classification on the long bone OM the authors concluded that the terms acute/chronic OM are unreliable and do not influence the diagnostic workup or the principles of medical or surgical management [29].

Given the great variability of definitions for acute and chronic OM existing in the literature, we conclude that these terms are impractical in most cases as they lack accuracy in describing the underlying disease, and cannot dictate the treatment plan or predict prognosis. An exception to the above conclusion is the pediatric cases of acute OM due to the greater capacity of the younger patients to absorb necrotic bone and, therefore, to potentiate the effects of medical treatment. Additional variation in the treatment plan between acute and chronic forms of OM is in the duration of antimicrobial treatment. Lima et al. concluded that in acute cases patients should be given initial empiric antimicrobial treatment followed by targeted treatment for three to six weeks, while chronic cases require up to six months of targeted therapy [7].

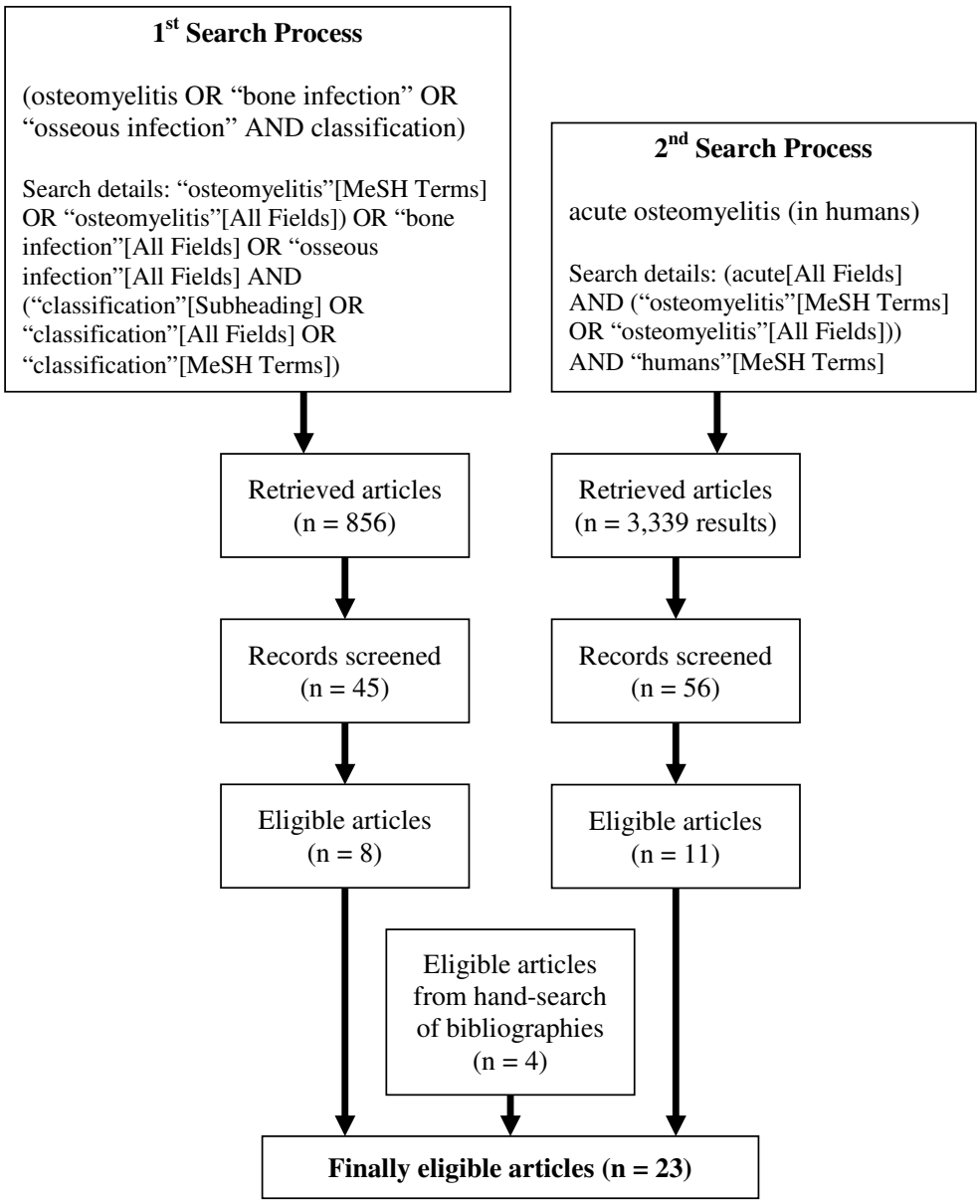

FIGURE 1. Search strategy flow chart.

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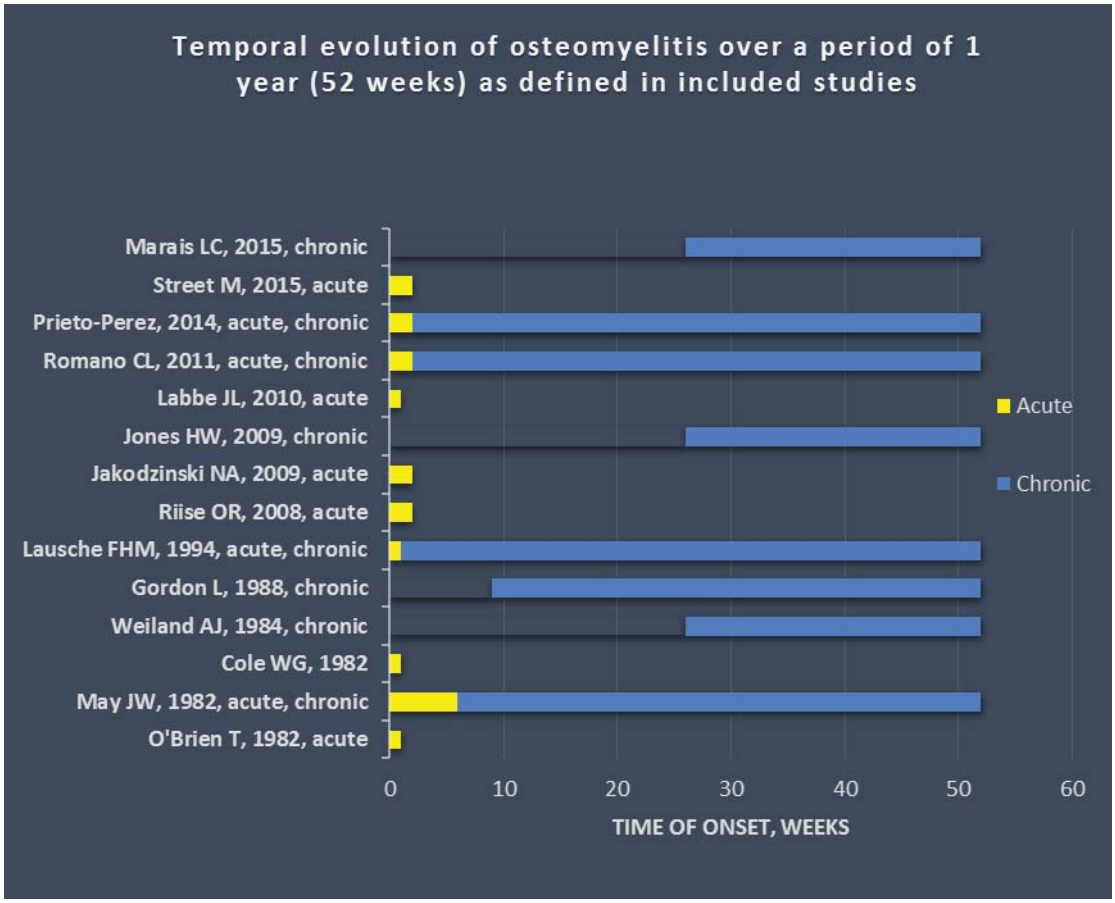

FIGURE 2. Temporal evolution of osteomyelitis over a period of one year as defined in included studies.

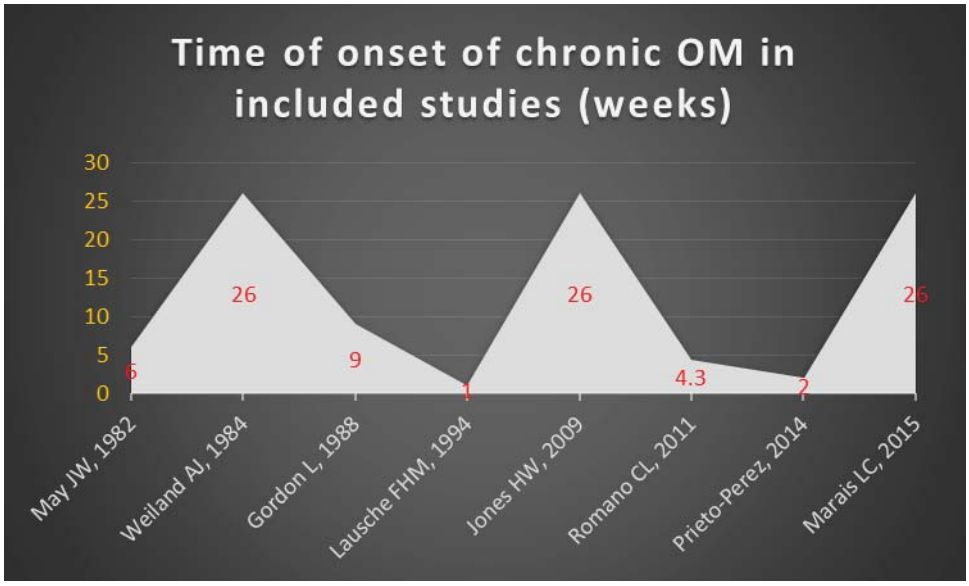

FIGURE 3. Time of onset (weeks) of chronic osteomyelitis, as defined in the included studies.

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QUESTION 5: Is synovial fluid or fracture hematoma always aseptic? If not, could this play a role in acute infection or periprosthetic joint infection (PJI) after open reduction and internal fixation (ORIF)?

RECOMMENDATION: Fracture hematoma is not always aseptic. It is unknown if synovial fluid is always aseptic. In addition, it is unclear if this plays a role in acute infection or fracture-related infection (FRI) after ORIF.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The association between soft-tissue conditions and infection has been well-known since the 1970s, when Gustilo and Anderson described how the major risk factor for post-traumatic infection following open fracture was the quality of the soft tissue envelope [1]. More recent evidence has demonstrated how traumatized host tissue can result in altered vascularization, decreased perfusion, increased endothelial permeability and decreased oxygenation; all of which can compromise the body's innate ability to resist local infection [1,2]. The prevailing theory of infection is that it is secondary to inoculation of pathologic microorganisms in traumatized tissues; however, it is unclear how infection occurs in closed trauma if there is no bacterial contamination through an open wound [2]. Some have questioned the common belief that synovial fluid and fracture hematoma is always aseptic based on evidence from other surgical fields that demonstrated how bacterial balance within presumably clean soft tissues affects the likelihood of soft tissue healing versus infection [3].

Two recent studies explored if fracture hematoma or callus was aseptic. In contrast to the prevailing view that these tissues are always clean, both studies found that 14 to 40% of the deep tissues grew bacteria when cultured, but no study has replicated these findings with synovial fluid. Szczesny et al. used conventional and molecular bacterial detection methods to determine if bacteria colonized lower limb soft tissues and bone following closed fractures in 71 patients. Cultures of fracture callus were positive in 26.7% of patients and bacterial rRNA was isolated in 41% of patients [4]. Similarly, Font-Vizcarra et al. evaluated the presence of positive cultures from hematoma in 109 patients with femoral neck fractures. They found that fracture hematoma was positive in 31.2% of all patients [2]. In both studies, the most common cultured organism was *S. epidermidis*. Based on recent basic science data, the presumed mechanism of infection of the deep tissues was that high-stress conditions resulted in decreased ability to contain skin and mucosal flora, leading to seeding of traumatized soft tissues/hematoma by lymphatic spread or transient bacteremia [1,2,4].

Although there is good evidence that fracture hematoma is not always aseptic, it remains unclear if the bacteria within the deep tissues play a role in acute infection or PJI after ORIF. Font-Vizcarra et al. did not find that culture positivity was a risk factor for early post-traumatic infection unless the specimen grew gram-negative rods [2]. Similarly, positive cultures from the fracture callus was not associated with non-union following closed tibia or femur fractures

[4]. Based on this data, it is unknown what bacterial load is necessary to evoke infection and overwhelm the host response [3].

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QUESTION 6: What is the relationship between implanted metal and colonization under a vacuum-assisted closure (VAC) in open fractures?

RECOMMENDATION: The use of negative pressure wound therapy (NPWT or VAC) over exposed orthopaedic implants has been reported but its role remains unknown. Furthermore, no evidence exists regarding the effect of NPWT on the colonization of metal implants in open fractures. Further research is required to provide more insight into this question.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

NPWT has emerged as a promising modality for the treatment of open fracture wounds between operative debridements and delayed wound closure or coverage [1,2]. Traditional management of fractures with soft tissue defects included wet-to-dry dressings with the risk of wound contamination and infection rates reportedly as high as 50% [3]. In addition to providing a semiocclusive dressing, NPWT mechanisms of action include stabilization of the wound environment, reduction of wound edema, improvement of tissue perfusion and stimulation of cells at the wound surface [1]. While initial randomized controlled trials (RCTs) favored NPWT in reducing infection in open fractures [4], a recent Cochrane database review found little difference compared to standard dressings [5]. The ability to successfully clear the infection may be tied to the VAC's effect on the wound bioburden [6].

A recent systematic review identified 24 studies investigating the topic of bacterial growth and NPWT, but none contained exposed implants [6]. The authors identified 10 experimental studies, 4 RCTs, 6 clinical studies and 4 using an instillation VAC system [6]. Of the RCTs, only one quantified bacterial proliferation and performed species analysis. Moues et al. found that NPWT selectively reduced non-fermentative gram-negative bacilli (NFGNB) but increased the proliferation of *S. aureus* [7]. The other three RCTs found no difference with the NPWT in regard to reduced bacterial growth or number of positive cultures [6]. The authors of this review concluded that there was a lack of concensus in the literature if the NPWT increases, decreases, or has no effect on the wound bioburden.

Perhaps even less is known about the relationship between implanted metal and colonization under a NPWT device in open fractures, as no studies have investigated this topic. The main reason is that contemporary "fix and flap" open fracture treatment does not advocate the use of NPWT devices over exposed metal. Some cases where this treatment might be an option include: (a) open fracture treated initially with hardware that undergoes wound breakdown, (b) if hardware removal at debridement is not feasible or would drastically compromise limb stability or (c) the patient is not a medical candidate for additional soft tissue coverage or additional surgery [8]. In such cases, the recommendation is to perform a secondary early coverage with local or distant flaps, but NPWT is not an option for definitive treatment. While case reports and small series have described the use of a wound VAC over exposed orthopaedic hardware in other instances [8–13], no studies have included bacterial proliferation or speciation analysis.

In conclusion, while there is evidence supporting the safety and efficacy of NPWT over exposed metal for a period of time without infectious complications, there are no published studies investigating this in associaton with open fractures. While the use of NPWT in open fractures with exposed metal is a viable option, it is not a part of the contemporary treatment of open fractures. Further research and study into implant colonization under a NPWT will be required before such a practice can be routinely recommended.

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Treatment

3.1. TREATMENT: ANTIBIOTICS AND NONOPERATIVE MANAGEMENT

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QUESTION 1: What is the most optimal prophylaxtic antibiotic coverage and treatment duration for open fractures of long bones?

RECOMMENDATION: The use of prophylactic antibiotics for open fractures of long bones has a protective effect against early infection. Antibiotics should be administered as soon as possible after the injury. The antibiotic of choice should target gram-positive organisms. Additional coverage for gram-negative organisms should be considered for patients with high-energy open fractures. Antibiotics should not be continued for more than 72 hours after wound closure.

LEVEL OF EVIDENCE:

- Efficacy of prophylactic antibiotics – Strong
- Timing of prophylactic antibiotics – Moderate
- Choice of antibiotics – Limited
- Treatment duration – Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Efficacy

Antibiotic administration has been shown to decrease the infection rate in open fractures in randomized controlled trials [1,2] as well as systematic reviews [3,4]. Patzakis et al. demonstrated for the first time the benefit of antibiotics in a prospective, randomized study [1], in which the infection rates for cephalothin versus penicillin with streptomycin versus no antibiotics were 2.3%, 9.7%, and 13.9%, respectively. In a Cochrane review data from 1,106 participants in eight studies were analyzed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.65, absolute risk reduction 0.07 [95% CI 0.03 to 0.10]). [3]. Another more recent systematic review also suggested a large, consistent reduction in infection risk with antibiotic use (RR 0.37, 95% CI, 0.21 to 0.66) [4].

Timing

In a retrospective study of type III open tibial fractures by Lack et al., administration of systemic antibiotics more than 66 minutes after injury was significantly and independently associated with deep infection (odds ratio (OR), 3.78, 95% CI, 1.16 to 12.31) [5].

Based on the quality and quantity of available evidence, the initial strength of the recommendation for early administration of antibiotics would be limited. However, we can upgrade this recommendation to one of moderate strength based on the following factors: (a) there is strong evidence that antibiotics need to be given and (b) delaying the necessary administration of antibiotics does not convey any benefit that could balance the potential risk of increased infection rate with delayed administration.

Choice of Antibiotics

Target organisms for prophylactic administration should be contaminants in the wound. Studies evaluating the microbiology of open fracture wounds have consistently shown that most contaminants are gram-positive organisms [6,7]. A study of 616 type I and II open fractures of the tibia reported that bacterial contamination at the fracture site consisted of a similar distribution of gram-positive (75 to 78%) and gram-negative (22 to 26%) species upon arrival at the emergency department, at the start of the operation, and at wound closure [6]. Methicillin-resistant *Staphylococcus aureus* (MRSA) were absent among the strains isolated at these stages [6].

The importance of antibiotics covering gram-positive organisms (usually a first-generation cephalosporin) is widely agreed upon. However, the necessity of coverage against gram-negative organisms or against anaerobes remains controversial.

No studies in the literature have directly compared gram-positive coverage to combined gram-positive and gram-negative coverage. Patzakis et al. recommended addition of aminoglycosides in all open fractures and reported a reduction in the infection rate from 14.6% in open tibias treated with a cephalosporin (from 1976 to 1977) to 4.5% in open tibias treated with both a cephalosporin and an aminoglycoside (1979 to 1980). However, this was not a direct comparison but instead a comparison of patients treated in different time periods in two prospective studies [8]. Gustilo et al. reported that 77% of cultures isolated from infected open fractures were of gram-negative bacteria and advocated addition of aminoglycosides for type III open fractures [9]. Similarly, Vasenius et al. in a randomized controlled trial of clindamycin vs. cloxacillin reported high surgical site infection (SSI) rates in type III open fractures and advocated addition of an aminoglycoside in these severe open tibia fractures [10].

Contamination of open fracture wounds with gram-negative organisms, although less frequent, still occurs [6,7] and a severe open fracture may be misclassified due to limitations in the interobserver agreement of the Gustilo-Anderson classification [11]. However, the SSI rates of Gustilo type I and II fractures have been consistently low in the literature even with narrow-spectrum antibiotics that mainly target gram-positive species [9].

Therefore, administration of a first-generation cephalosporin is recommended for Gustilo I and II fractures [12–14] and additional administration of an antibiotic with good gram-negative coverage is recommended in Gustilo type III (e.g., aminoglycoside or 3rd generation cephalosporins) [13,14,15,16]. Aminoglycosides may cause nephrotoxicity, especially in the setting of renal disease or dysfunction; therefore, renal function should be considered beforehand. Pannell et al. reported that gentamicin use during treatment of open fractures does not lead to increased rates of renal dysfunction when used in patients with normal baseline renal function [17]. Unfortunately, renal function is often not known at the time of initial admission of antibiotics.

Anaerobic coverage (e.g., penicillin, clindamycin or metronidazole) is recommended in the presence of potential clostridial contamination (e.g., fecal contamination or farm-related injuries) [13,14]. However, no study has compared anaerobic coverage in such injuries. A group developing guidelines for combat injuries that are severely injured and contaminated did not recommend anerobic coverage, but instead emphasized early and thorough debridement.

The emergence of antimicrobial resistance in bacteria has created concerns about the adequacy of current antibiotic protocols, especially against MRSA. However, a randomized controlled trial comparing vancomycin and cefazolin versus only cefazolin in 101 patients with open fractures found no difference in the infection rates between the groups: 19% in the group receiving vancomycin and cefazolin versus 15% in the cefazolin only group [18]. As a result, the routine use of vancomycin in open fractures cannot be recommended based on available data.

Duration

Two randomized controlled trials compared one to five days of antibiotics in the management of open fractures [6,19]. Both studies reported that the infection rates were similar in the one-day and the five-day groups and advocated against the prophylactic administration of antibiotics for five days. However, no randomized controlled studies have compared one-day, two-day, or three-day antibiotic prophylaxis. A retrospective case control study of 1,492 open fractures by Dunkel et al. showed after multivariate analysis that there was no significant difference in infection risk for one-day prophylaxis compared with longer regimens [20]. Although the OR for infection in the two/three-day group compared to the one-day group was 0.6 (95% CI, 0.2 to 2.0) in all fractures and 0.3 (95% CI, 0.1 to 3.3) in type III fractures. These lower ORs were not found to be significant.

Prolonged prophylactic administration of antibiotics beyond 72 hours is not recommended. In the absence of additional data for type I and II open fractures we would recommend administration of antibiotics for at least 24 hours after wound closure, but not to exceed 72 hours. In type III fractures we recommend 72 hours of antibiotic administration or 24 hours after closure or soft tissue coverage of the wound, in agreement with existing guidelines [13,15,16,21].

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QUESTION 2: What antibiotic(s) should be used for low-energy open fractures? What antibiotic(s) should be used for high-energy open and grossly-contaminated fractures?

RECOMMENDATION:

1. Antibiotic treatment targeting gram-positive organisms is recommended as soon as possible for all open fractures; low- and high-energy.
2. In high-energy or grossly-contaminated open fractures, additional antibiotics should be considered for gram-negative coverage.

LEVEL OF EVIDENCE: 1. Strong; 2. Limited

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

RATIONALE

Open fractures are those that occur with associated skin and overlying soft tissue disruption, resulting in communication between the fracture site and the external environment [1]. The amount of energy imparted to an extremity during trauma results in a greater or lesser degree of bone and soft tissue compromise. Many authors have attempted to use different classifications to correlate the degree or amount of energy and the tissue compromise. The most commonly used is one described by Anderson et al. [2], later modified by Gustilo et al. [3]. For the purpose of this document, this definition will be used and correlated with the degree of energy associated. According to this classification, type I fractures are characterized by a wound of < 1 cm with minimal contamination, comminution and soft-tissue damage (these are low-energy). Type II features lacerations of > 1 cm and moderate soft- tissue injury, but wound coverage is adequate and periosteal stripping is not extensive (moderate energy). Type III fractures are divided into three subtypes and are all considered as high-energy. Type IIIA is characterized by high-energy trauma, extensive soft-tissue damage and substantial contamination, but wound coverage remains adequate after debridement has been completed. Type IIIB displays inadequate wound coverage following debridement and coverage procedures are required. Type IIIC is an open fracture associated with an arterial injury requiring repair.

One of the main purposes of this classification, besides description, is the correlation with infection rates which have been shown to increase correspondingly [4]. Rates of infection have been reported to range from 0% to 2% for type I, 2% to 5% for type II, 5% to 10% for type IIIA, 10% to 50% for type IIIB, and 25% to 60% for type IIIC3 [2,3,5]. Prophylactic antibiotics have become a standard for open fractures since 1974 when Patzakis et al. [6] demonstrated in his prospective study that cephalothin had significantly lowered the infection rate to 2.3 % compared with 13.9% in the control group. This finding was later confirmed by a systematic review demonstrating that the use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo [7].

The efficacy of first-generation cephalosporins for open fractures has been confirmed in level I and II studies [7,8]. As initially reported by Gustilo et al. [3], type III fractures had a high rate of gram-negative infections, which supports the addition of an aminoglycoside or a third-generation cephalosporin. A different, prospective randomized study of severe open tibia fractures (type II and III) comparing first-generation cephalosporin and third-generation cephalosporin showed no statistical difference in the rate of infection [9]. *The Surgical Infection Society Guideline: Prophylactic Antibiotic Use in Open Fractures: an Evidence-Based Guideline* recommends the administration of first-generation cephalosporin for 24-48 hours preoperatively as a safe and effective prophylactic choice in patients with type I open fractures [10]. The *East Practice Management Guidelines Work Group: Update to Practice Management Guidelines for Prophylactic Antibiotic Use in Open Fractures* recommends that preoperative antibiotic prophylaxis for coverage of gram-positive organisms should begin for patients with open fractures as soon as possible after injury [11]. For type III fractures, additional coverage for gram-negative organisms may be given as these fractures are considered highly contaminated, although this aspect is not yet clearly supported by high-level studies [12].

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QUESTION 3: What is the optimal mechanism for delivery of local antibiotics in contaminated or infected wounds?

RECOMMENDATION: There is moderate evidence to support the use of local antibiotic delivery in contaminated or infected wounds. Future data collection seems important to improve our knowledge on this topic.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 75%, Disagree: 15%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

The evidence regarding the optimal mechanism for delivery of local antibiotics in contaminated or infected wounds is moderate. Open limb fractures are often associated with considerable bone damage including periosteal stripping, extensive soft-tissue trauma and severe contamination [1,2]. This enables bacteria to establish a fracture-related infection (FRI) by breaching the damaged skin barrier and adhering to non-living surfaces, such as implants or dead bone fragments [3]. FRI, which occurs up to 30% of cases after complex open fractures, is the one of the most significant complication after fracture fixation and is associated with a significant socio-economic impact [4,5]. Therefore, one of the main objectives in the management of open fractures is infection prevention [6]. Overall, current evidence on the local application of antibiotics in the prevention of FRI is limited. Moreover, comparative studies on local antibiotics and carriers are nonexistent.

With this in mind, a recent comprehensive literature search was performed in PubMed, Web-of-Science and Embase [7]. Cohort studies investigating the effect of additional local antibiotic prophylaxis compared to systemic prophylaxis alone in the management of open fractures were included and the data were pooled in a meta-analysis. Following screening and confirmation of eligibility, 18 articles were available for analysis. Further review of these studies revealed the absence of a control group in 10 case-series. Finally, eight studies [8–15] with a total of 2,738 patients were eligible for quantitative synthesis. The effect of antibiotic loaded polymethyl methacrylate (PMMA) beads was investigated by six [8–13] of these studies and two [14,15] studies evaluated the effect of local antibiotics applied without a carrier. Meta-analysis showed a significantly lower infection rate when local antibiotics were applied than in the control group receiving standard systemic antibiotic prophylaxis alone. This effect was present in all three main Gustilo-Anderson types. However, when evaluated by the 'Grading of Recommendations Assessment Development and Evaluation (GRADE)' approach, it appeared that these results should be interpreted with caution due to the low rating of the recommendation.

This low rating implies the uncertain impact of heterogeneity and bias on the pooled data results [16]. Most studies used PMMA as a carrier for application of local antibiotics. The studies by Henry et al. [8] and Ostermann et al. [9,10] found a beneficial effect of locally applied tobramycin PMMA beads. This finding was supported by Keating et al. who reported a trend towards reduced risk of FRI with the addition of local tobramycin-loaded PMMA beads [11]. Ziran et al. also investigated the effect of tobramycin-loaded PMMA beads and reported a two-fold risk reduction in infection rate (31.3% vs. 16.7%) [12]. However, due to the small sample size, the study is associated with a considerable risk of bias and its results should be interpreted with caution. Conversely, the only randomized control trial (RCT) in this meta-analysis did not find any beneficial effect in preventing FRI with the use of tobramycin-loaded PMMA beads and even reported an increased risk of FRI (8.3% vs. 5.3%). However, this study, conducted by Moehring et al., is associated with a considerable risk of bias due to patient prognostic factors not being reported, inadequate case matching with regards to Gustilo-Anderson type and the absence of a clearly defined primary outcome [13].

Two studies investigated the effect of local antibiotics without a carrier [14,15]. In open articular tibial fractures, Singh et al. found no beneficial effect of topical vancomycin, although this study is associated with a considerable risk of bias due to a small sample size, inadequate reporting of soft tissue involvement and length of follow-up [14]. The advantages of topical vancomycin include widespread availability, low costs, efficacy against most common pathogens and limited concerns regarding inhibition of bone healing or osteogenic cytotoxicity [17]. However, there are concerns that in the age of widespread antimicrobial resistance, the use of vancomycin should be reserved for therapeutic, rather than prophylactic, purposes [15].

Lawing et al. investigated the effect of locally injected aqueous aminoglycosides in open fractures in a methodologically well-designed observational trial. They found a significantly reduced infection rate (9.5%) compared to the control group (19.7%). There was no obvious evidence that local aminoglycosides were inhibiting bone healing since they were not associated with a higher non-union rate [15]. O'Toole et al. recognized the missing evidence of topical vancomycin in extremity fractures as well and recently published a study outline of a planned multicenter RCT investigating its effect on FRI [17]. A qualitative analysis was performed on the ten studies [18–27] that were excluded from the meta-analysis for a lack of control group. Five of these studies investigated the effect of PMMA containing tobramycin [19,20,27] or the combination of tobramycin and vancomycin [21,23] and reported an infection rate from 0% to 20.0%. Chaudhary et al. assessed the efficacy of gentamicin impregnated collagen fleece in the treatment of open fractures in a case-series of 31 patients and reported an infection rate of 16.1% [25]. Cai et al. observed no infection in 26 open long-bone fractures treated with local vancomycin loaded calcium-sulfate pellets [24]. Three series reported no deep infection after treating in total 22 open tibia fractures with a poly (D,L-Lactide) (PDLLA)/gentamicin coated tibial nail [18,22,26].

Overall, we can state that most evidence regarding local antibiotic carriers is limited to studies using local PMMA beads. Indeed, antibiotic impregnated PMMA beads should not be neglected in the acute management of open fractures. PMMA is non-biodegradable and therefore requires surgical removal, which limits its application to cases that need a planned second-look operation. In addition, following the initial high antibiotic level release from PMMA, there is a prolonged low-level antibiotic release that may be below minimum inhibitory concentration (MIC) for potential pathogenic

organisms. This might initiate a selection pressure that favors the emergence of resistant strains, as well as a foreign body reaction [28]. As mentioned earlier there were also studies included in this review that administered antibiotics without a carrier. The main disadvantage of locally administered antibiotics without a carrier is that there is no controlled delivery of antibiotics directly into target tissues and no sustained release over a sufficient time interval [28]. Biodegradable carriers overcome this issue and do not have the limitations of PMMA. New absorbable biocomposites, such as gentamicin-loaded calcium-sulfate/hydroxyapatite, have shown to be highly effective in treatment of chronic osteomyelitis [29]. Malizos et al. demonstrated in a recently-published multicenter RCT that a fast-resorbable antibiotic loaded hydrogel significantly reduced infection rates after internal osteosynthesis of closed fractures [30]. However, evidence in clinical literature on the effectiveness of degradable carriers in open fractures is limited. Our literature search identified only five case-series analyzing the effect of biodegradable antibiotic carriers in open fractures. Even though these studies are associated with a considerable risk of bias, the overall results are promising: no infections were reported in 26 open fractures treated with vancomycin loaded calcium-sulfate pellets [24] and in 22 open tibia fractures stabilized with a gentamicin coated tibial nail [18,22,26]. The study by Chaudhary et al. did report some infections with the use of antibiotic impregnated collagen fleece [25].

In conclusion, this systematic review is providing an overview of most recent literature on local antibiotic prophylaxis in open long-bone fractures, including various new absorbable carriers [28,30,31]. The beneficial effect of local antibiotics in open limb fractures was proven by pooling data exclusively from cohort studies that compared the effect of additional local antibiotics to standard systemic antibiotic prophylaxis. With respect to the type of carrier that should be used, most available evidence exists on antibiotic-loaded PMMA beads. As PMMA has potential downsides, multiple biodegradable carriers have been recently developed and some of the new carriers seem promising (e.g., poly [D,L-Lactide] [PDLLA]/gentamicin coating, fast-resorbable antibiotic loaded hydrogel). The main limitation of this review and meta-analysis is the low quality of evidence available in the literature. RCTs of sufficient statistical power and bias limiting methodologies are required to corroborate the findings of this meta-analysis. Of critical importance is the reporting of trials in accordance to agreed minimum datasets and, in particular, the use of a standardized definition for FRI [32].

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QUESTION 4: Is there a role for a combination of local and systemic antibiotic delivery systems to treat open fractures with overlying contaminated wounds?

RECOMMENDATION: The administration of systemic antibiotic and a local antibiotic delivery device (system) is an effective treatment strategy for open bone fractures with contaminated wounds.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 4%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The use of local antiseptic or antibiotic in the treatment of open bone fractures for infection prevention has a history of over 100 years, and this treatment approach continues today [1,2]. The use of systemic antibiotics for the treatment of open bone fractures is supported by landmark clinical studies by Patzakis, Harvey and Ivler, as well as Gustilo and Anderson [3,4]. Their early studies indicated that systemic antibiotic treatment was therapeutic and prophylactic in preventing wound infections in open bone fractures.

With the development of the addition of antibiotics, first in bone cement and later in other biomaterials, local antibiotic delivery for the treatment of open bone fractures became a therapeutic option for infection prevention [1,4–8]. While several recent reviews by Isaac et al., Warrender et al. and Gosselin et al. support the role of systemic antibiotic delivery in the treatment of open bone fractures [9–11], the 2014 systematic review by Craig et al. directly addresses the role of systemic and local antibiotic delivery in open tibia bone fractures [12]. Their study conclusion was,*"The findings support consideration of augmenting the antibiotic prophylaxis regimen to include locally delivered antibiotics. Patients with severe fractures will obtain greatest benefit from infections avoided"* [12]. Another key comment in the Craig et al. study conclusions is, *"No trial directly compared the two treatments for open tibia fractures, limiting the ability to attribute the differences in observed infection rates directly to the treatments themselves.* ***A large comparative study to improve the evidence on relative effect size is merited****"* [12]. A more recent meta-analysis by Morgenstern et al. concluded that there is a risk reduction with respect to infection of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. Although the authors stated that due to limited quality, heterogeneity and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution [13].

Despite the lack of the mentioned direct comparison study and many other technical questions that range from antibiotic therapy duration to antibiotic selection, several retrospective studies do support the combination of systemic and local antibiotic delivery for infection prevention during the treatment of open bone fractures.

Limitations

- Used only English language journal articles for review

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QUESTION 5: What is the most optimal antibiotic treatment for chronic osteomyelitis?

RECOMMENDATION: Antiobiotic selection should be culture-specific, if possible. No clear evidence exists to suggest that longer duration of therapy (12 to 16 weeks) is superior to shorter duration (4 to 6 weeks). In addition, there is no evidence to support the proposition that intravenous (IV) antibiotic treatment is superior to oral treatment.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Chronic osteomyelitis remains a challenging problem in 2018. Recurrence of infection is common with a reported incidence of 20 to 30% [1,2]. The disease includes a vast spectrum of clinical scenarios that range from mandibular osteomyelitis arising as a result of dental complications, chronic vertebral osteomyelitis, post-surgical and post traumatic long bone osteomyelitis, pressure related chronic osteomyelitis of the pelvis, calcaneus and other sites as well as diabetic foot infections. Other disease processes also could be included in this group. Complicating the picture is the fact that these infections are caused by a multitude of pathogens and may be polymicrobial. Management of chronic osteomyelitis usually requires surgical debridement plus antibiotic therapy [3]. Because of variations in surgical approaches and the recent use of local antibiotic delivery devices, recent literature contains multiple variables that are difficult, if not impossible to control for, to determine what influence the systemic antibiotic played in the patient's outcome.

Antibiotic Choice

Older literature that includes randomized control trials (RCTs) often used an oral quinolone with a comparator parenteral agen [4–7]. Gentry and Rodriguez prospectively compared ciprofloxacin with cephalosporin or nafcillin plus aminoglycoside in 31 patients with biopsy proven osteomyelitis. These two populations had similar success rates of 77% and 79% respectively [4]. Mader et al. evaluated 26 patients with chronic osteomyelitis with oral ciprofloxacin vs. "standard parenteral therapy" consisting of nafcillin, clindamycin and gentamicin singularly or in combination. Both groups had similar success rates when evaluated two to three years after treatment [7]. Gentry and Rodriguez compared 19 patients with oral ofloxacin for 8 weeks with 14 patients with parenteral antibiotics for 4 weeks and found 74% and 86% success rates, respectively [5]. Gomis et al. evaluated 32 patients who had susceptible chronic osteomyelitis with oral oflaxacin versus imipenem-cilastin and found cure rates of 69% and 50%, respectively which were not statically significantly different [6]. Euba et al. compared 50 patients with Staphylococcal osteomyelitis comparing rifampin and clotrimoxazole combined versus IV cloxacillin for 6 weeks with oral cloxacillin for 2 weeks. Treatment outcomes in these two groups were similar and not statistically significantly different [8]. Norden et al. compared 19 patients with chronic post-traumatic chronic osteomyelitis using IV Nafcillin or cephalothin with IV nafcillin plus rifampin and found that cure rates were higher in the IV nafcillin plus rifampin group but this was not statistically different [9]. In the final RCT, Sheftel et al. studied ceftazidime vs. ticarcillin plus tobramycin for chronic gram-negative osteomyelitis in 18 patients and found cure rates of 67% and 89%, respectively [10].

Finally, Spellberg and Lipsky published a review of systemic antibiotic therapy for chronic osteomyelitis in Clinical Infectious Disease in 2012 [11]. Included in that summary were 49 non-RCTs that included 9 to 115 patients in each study with most studies having 20 to 40 patients each. The study populations were diverse and included patients with and without infected prostheses [11]. Surgical intervention was not universal in the studies and follow up was variable. Despite these limitations, some lessons can be learned. In the nonrandomized studies that included four to six weeks of a parenteral ß-lactam, the cure rates were 60-90% [1]. Cure rates were lower in patients that had chronic osteomyelitis with Pseudomonas [11]. Cure rates were also lower in studies where vancomycin was compared with ß-lactam agents for osteomyelitis caused by *S. aureus* [11]. Fluoroquinolones were the best studied antibiotic group for chronic osteomyelitis. Most studies reported cure rates of 60-80% [11]. Rifampin also improved outcomes in several studies when combined with fluoroquinolones and other active agents for chronic *S. aureus* osteomyelitis [11]. However, because of the numerous drug interactions with rifampin, there are times when it is not advisable to use rifampin. In addition, rifampin should never be used without another known active agent due to the rapid development of rifampin resistance that often occurs within just a few days. Regardless, the authors of this review were unable to recommend the best agent for treatment [11].

Duration of Administration

Traditionally, six weeks of parenteral antibiotic therapy was prescribed for chronic osteomyelitis combined with surgical debridement [12,13]. Yet there is no clear advantage in the literature that longer durations result in better treatment success than shorter durations. In a recent systematic review, most of the included antibiotic therapy that was given was high-dose and administered for 12 to 16 weeks [11]. However, the available data in these studies is inconclusive to know if the higher doses or prolonged therapy improved outcomes [11]. At this time, the literature does not offer adequate evidence to determine the optimal duration of antibiotic therapy for chronic osteomyelitis [2,11,14,15].

Route of Administration

Recent evidence has shown that oral antibiotic therapy may be equally as effective as parenteral antibiotic therapy [2,11,15]. Conterno et al. conducted a Cochrane systematic review on antibiotics for treatment of chronic osteomyelitis in adults [2]. This review included RCT or quasi-RCTs regarding antibiotic treatment used after surgical debridement of chronic osteomyelitis in adults. They found no difference between oral and parenteral antibiotic therapy. This review was an update of a prior 2009 Cochrane review [16]. They concluded that the quality of evidence available was limited to make a definitive conclusion regarding antibiotic treatment of osteo-

myelitis [2]. In the aforementioned review, Spellberg and Lipsky suggested that chronic osteomyelitis can be effectively treated based on the antibiotic susceptibility of the pathogen(s) and pharmacokinetics with oral antibiotics as well as parenteral therapy. They concluded that oral antibiotic therapy with the proper agent was an effective alternative to parenteral antibiotics [11].

Conclusion

While the studies to date do not provide a clear optimal antibiotic choice, duration or route of administration for the treatment of chronic osteomyelitis, some observations are consistent from the data available. First, knowing the pathogen, pathogen sensitivities, antibiotic bone penetration and antibiotic toxicities do help the treating physician make the best choice for a specific patient and clinical scenario. It is important, whenever possible, to establish a microbiological diagnosis (or at least to obtain adequate bone tissue for culture in the lab) prior to initiating antibiotics. As the current recommendation for duration of therapy is typically 4-12 weeks, antibiotic exposure and toxicity can be significant. Second, in certain situations, oral therapy is just as effective as parenteral therapy and there are more studies supporting oral therapy than parenteral therapy. There is sufficient data to support the use of an active oral fluoroquinolone for osteomyelitis caused by gram-negative organisms, the use of an active fluoroquinolone with rifampin for *S. aureus* osteomyelitis, and the consideration of using trimethoprim-sulfa with rifampin for *S. aureus* osteomyelitis if both agents are active. Using an active fluoroquinolone alone for *S. aureus* osteomyelitis should be avoided due to the development of resistance while on monotherapy and the higher rate of relapse after therapy is completed. Third, adding rifampin to a variety of antibiotics seems to improve cure rates when coupled with another known active agent when treating *S. aureus* osteomyelitis. Fourth, surgical debridement and removal of infected hardware, when possible, generally improves treatment outcomes. Fifth, oral clindamycin which is routinely used for the treatment of acute *S. aureus* osteomyelitis in children [17–20], has not been well studied for the treatment of chronic osteomyelitis in adults. Finally, it is also important to keep in mind that antibiotics are only effective when they reach the site of infection. Adequate vascularized soft tissue coverage of infected bone, debridement of any significant necrotic tissue and sequestrum, and adequacy of blood flow to the affected site are likely critical factors in improving outcomes.

Clearly, additional RCTs are needed to answer the question regarding the optimal agent, route and duration of therapy for treating chronic osteomyelitis in adults.

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QUESTION 6: What is the recommended suppressive antibiotic therapy for the treatment of chronic osteomyelitis after fracture fixation when the implant cannot be removed?

RECOMMENDATION: Suppressive therapy with culture-specific antibiotics is aimed at allowing fracture healing prior to implant removal and definitive infection management.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after surgical treatment of fractures is a complication with significant morbidity, and in rare cases even mortality. Infections have often been classified according to the time interval between surgery and occurrence, although the distinction between acute and chronic infections has recently been challenged. Early infections are mainly caused by virulent microorganisms, such as *Staphylococcus aureus*, and diagnosed within the first three weeks of surgery. Delayed infections are typically due to less virulent bacteria, such as coagulase-negative Staphylococci, and develop between 3 and 10 weeks. Finally, late infections, occur after 10 weeks and are either caused by haematogenous seeding or by recurrence of inadequately-treated early infection [1]. Infections that occur following open reduction internal fixation (ORIF) are typically caused by biofilm-forming bacteria, which adhere to the implants [2]. In approximately one week, a mature biofilm already forming, which makes it less likely to for antibiotics alone to eradicate bacteria [3].

Common treatment for implant-related infection obeys to three established principles: surgical debridement, antibiotic therapy and eventual implant removal or staged exchange. However, in ORIF and with fracture-related infection (FRI), implant removal is unsuitable because of resulting fracture instability that often leads to prolonged infection [4,5]. This has consequences for the other aspects of treatment – if the implant is retained, the biofilm remains. Surgical debridement can remove the bulk of the bacterial load, but adjuvant antibiotic therapy must be directed towards the biofilm present. If the implants are retained, treatment consists of thorough surgical debridement, tissue cultures and long-term antibiotic suppressive therapy with rifampin-based combination antibiotic therapy. To date, only two classes of drugs have shown the properties that are needed for control of biofilm forming bacteria. Rifampin and other rifamycins act on biofilm active Staphylococci [6–11] and fluoroquinolones on gram-negative bacilli [12,13].

In the event of retained hardware after debridement of an acute infection following ORIF, the recommended antibiotic combination therapy should start immediately after the first surgical intervention and consists of 10 days of intravenous (IV) vancomycin and rifampin. Vancomycin was the agent of choice for empirical therapy because of its activity against a broad spectrum of microorganisms, the high incidence of gram-positive infections and the synergetic effect with rifampin [14–16]. Vancomycin therapy was started twice daily (1,000 mg IV), and was adjusted to maintain serum levels between 15 and 20 mcg/ml. Rifampin was given twice daily (450 mg IV). After tissue cultures identify the responsible bacterial pathogens and susceptibility data becomes available, vancomycin therapy can be switched to another, narrow spectrum antibiotic as indicated. Rifampin is continued unless rifampin-resistant bacteria are found.

Zimmerli et al. [2,6] assessed the effectiveness of this protocol in a randomized controlled trial, and after the IV administration period, oral combination antibiotic therapy with rifampin was continued for ten additional weeks. They reported 100% success in cases where both antibiotics were administered compared to 58% success when only ciprofloxacin was received. Barberan et al. [17] and Drancourt et al. [18] also studied infection following ORIF and evaluatied the effect of antibiotic combination therapy with rifampin reporting good results. Drancourt et al. [18] analyzed both periprosthetic joint infection (PJI) and FRI treated with initial retention and combination antibiotic therapy, and reported a success rate of 48% after an average follow-up of 23.5 months. The study of Barberan et al. [17] only included patients with infections following ORIF and demonstrated a success rate of 72%. In a prospective observational cohort study, Tschudin-Sutter et al. [19] analyzed 233 patients with orthopaedic implant-related infections of which 52.4% (122/233) were infections related to ORIF, for which the success rate was 90.2% (110/122) with the use of rifampin-combination regimen as suppressive therapy. This was seen on patients with implant retention after two years of followup. Patients were identified for inclusion using strict selection criteria (the duration of clinical symptoms was no longer than three weeks): stable implant, intact soft tissues, no abscess or sinus tract and the causative pathogen was susceptible to antibiotics with activity against surface-adhering microorganisms (i.e., rifampin for *S. aureus* or coagulase-negative Staphylococci and ciprofloxacin for gram-negative pathogens) [19]. This is so far the largest study evaluating patients with implant-associated infection managed with retention and long-term suppressive antibiotic therapy.

It is important to highlight the critical aspect of implant stability, as loose implants cannot be retained even if infection becomes evident at very early stages. Worlock et al. [4] demonstrated in a rabbit model that unstable tibial fractures were associated with significantly higher rates of osteomyelitis than those which were stable. These implants can often be retained when an acute infection develops after fracture fixation. Implant removal is generally undesirable in cases of acute infection as ORIF serves two different goals. First, the stability achieved by fixation is critical for fracture healing. When conditions are created in which micromotion between bone fragments is possible, resorption and necrosis of the affected bone will occur [5]. Second, the aim of operative fracture management and early mobilization is to prevent loss of function due to scarring of the surrounding soft tissue or joint stiffness. Special consideration should be given to infections after intramedullary fixation, with the popular belief that eradication of the infection is not feasible without implant exchange [20]. Chen et al. [21] reported on 23 infections following intramedullary (IM) nailing of the femur for fractures. The patients were divided into two groups where one group with IM nails had their nails removed and an external fixator was placed. All femur fractures with retained IM nails healed (12/12) and were infection free at followup of average 25 months. Only 7 of 11 patients (64%) in the external fixator group healed. Whereas removal or exchange of the implant provides the opportunity to remove the biofilm and thus reduce the bacterial load, in cases of implant retention the surgical debridement and adjuvant antibiotic therapy play a more important role.

In conclusion, in the situation of FRI where debridement and implant retention is chosen as the treatment strategy, rifampin (rifamycins) can be an effective adjuvant agent in suppressing gram-positive organisms while ciprofloxacin (fluoroquinolones) can be effective in suppressing gram-negative organisms.

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QUESTION 7: Is there a role for hyperbaric oxygen therapy (HBOT) and other non-antibiotic methods for the treatment of chronic osteomyelitis/implant infections?

RECOMMENDATION: There is limited evidence for the efficacy of hyperbaric oxygen (HBO) in the treatment of post-traumatic bone infections.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 5%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

HBOT has been proposed as an adjunctive therapy in the management of refractory osteomyelitis, which was defined as chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where acute osteomyelitis has not responded to accepted management techniques [1]. The procedure involves the intermittent inhalation of 100% oxygen in chambers pressurized above one atmosphere absolute (typically to about 2 to 2.5 atmosphere absolute (ATA)). It is based on the premise that increased tissue oxygen levels will enhance healing. Although adverse events are typically self-limiting, more serious potential complications include baro-traumatic otitis, pneumothorax, myopia and seizures [2].

While initially there was some enthusiasm about the use of HBOT in refractory osteomyelitis, this appears to have waned with only one case series published since 2004 [3]. Prior to this, a small number of descriptive studies were published that reported encouraging results [4,5]. A systematic review by Goldman in 2009 examined the evidence for HBOT in wound healing and limb salvage. Five studies were classified as "moderate" strength evidence (the remaining 10 being either "low" or "very low") [6]. In the first of these Morrey et al., reported on the outcomes of HBOT in 40 patients who had recurrent infection for more than 6 months after at least 1 surgical procedure [7]. Following surgery, antibiotics and HBOT, 85% of patients were reported to be disease-free at one year.

Davis et al. performed a retrospective study on 38 patients with actively draining wounds and at least 1 failed previous surgical procedure [8]. Complete healing was achieved, again in combination with surgery and antibiotics, in 89% of cases. From 1998 to 2004 Chen et al., published three overlapping case series involving patients who presented with recurrence of infection following prior surgical treatment [9–11]. The success rate of standard treatment, involving aggressive debridement, antibiotics and HBOT, was reported as 79% to 92% (note that the 2003 study was not included in the Goldstein systematic review). The findings from all of these non-comparative studies are however difficult to interpret and confounded by the fact that HBO was used as part of a multi-modal treatment strategy. Furthermore, it is not clear if the initial failed surgical procedures were performed by experienced musculoskeletal infection surgeons. There was only one comparative study included in the Goldman systematic review. Esterhai et al. performed a prospective non-randomized controlled trial and found that HBOT had no effect on length of hospitalization, initial clinical outcome or the late recurrence of infection [12]. The only clinical study published since the systematic review in 2009, described the experience of a single center with HBOT in general and did not provide a detailed description specific to the chronic refractory osteomyelitis patients [3].

Recently, the effect of HBOT on implant-associated infection was further drawn into question. Büren et al. illustrated in a standardized murine model that HBOT did not have a beneficial effect on the local infection or the immune response to the infection compared to standard therapy alone [13]. Interestingly, they also noted delayed bone healing and a higher rate of non-unions at 28 days in the HBOT group. Ultimately, there is currently only limited evidence

supporting the use of HBOT in post-traumatic infections and the single study with a control arm reported no benefit.

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3.2. TREATMENT: SURGEON AND CARE TEAM

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QUESTION 1: Should all infected non-unions be treated in specialized septic centers?

RECOMMENDATION: The current literature, although rich in case series and observational studies, does not lend support to the recommendation that "specialized septic surgery centers" should care for infected non-unions. However, because of the complexities of infected non-unions, care in specialized centers may yield the best possible outcome.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 70%, Disagree: 21%, Abstain: 9% (Super Majority, Weak Consensus)

RATIONALE

Infected nonunion is the persistence of an infection at the fracture site and the surrounding tissue and failure of bone healing for eight months, (U.S. Food and Drug Administration). It could be considered as an osteomyelitis at an unstable fracture before the debridement and which remains unstable thereafter. It is commonly accompanied by soft tissue problems, adjacent joint stiffness, motor and sensory dysfunction of the limb, chronic pain, depression and unrelated medical problems leading to considerable physical, social, financial and mental impact on the life of the patient and the healthcare systems and may even become a limb-threatening complication.

Bone healing and eradication of the infection is the main but not the only objective because a non-functional and deformed limb with pain and stiffness of the adjacent joints will be an unsatisfactory outcome even if at some point the bone heals sufficiently. Treatment is aimed at returning the extremity and the patient to the fullest function possible during and after the treatment process. This process is usually long-lasting and must be planned accordingly so that in case of failure, further treatment alternatives remain available. Because of the various nonunion types and the multitude of possible problems related to the patient's health and comorbidity, such as prior treatments and the bone and soft tissue defects, no simple treatment algorithms are possible. The recommended strategy, with an array of management alternatives, is: (a) the "infection-elimination first" by local radical debridement of all pathological tissue, followed by (b) tissue and bone reconstruction and (c) targeted chemotherapy with local and systemic antibiotics.

A specialized team of orthopaedic surgeons with expertise in a broad spectrum of techniques must thoroughly evaluate the patient and carefully consider all available information about the general health status and the local tissue conditions. The prior failed treatments must be taken into account, as well as the optimization of all treatment modifiers. Where extensive surgical exposures have failed consideration is given to less invasive techniques that respect the surrounding soft tissues. Stable fixation, adequate vascularity, bone-to-bone contact, and bone grafting or strong bone regenerate are crucial factors for success. The potential need for future treatment should be considered when pursuing any particular intervention.

The care of the patients with infected nonunions may be best performed at specialized septic surgery centers with an expert team approach to achieve the ultimate goals of bony union and restoration of alignment and function, while limiting the extent of residual disability. A medical center that treats infected nonunions should provide all of the appropriate resources and a supportive team of consulting specialists to contribute to all aspects of care, both at the initial evaluation and throughout the course of treatment. The role of anesthesiologists is obvious as well as of the internists for patients with serious medical conditions. Plastic surgeons are often necessary to reconstruct the soft tissues

after serial debridement and vascular surgeons may be required if the vascularity of the limb is in question. A multidisciplinary treatment team should be utilized in providing comprehensive care, including a pain management specialist, a psychiatrist to support patients with clinical depression, a neurologist to evaluate motor or sensory loss, a dietician to optimize the nutritional status, and physical and occupational therapists to facilitate rehabilitation. Microbiology and histopathology labs with the availability of modern diagnostic facilities, an experienced clinical pharmacologist and an infectious disease specialist are all integral parts of the multidisciplinary unit as well.

APPENDIX - SEARCH STRATEGY

There is no study in the literature that has evaluated this particular issue. We have conducted a broad literature search trying to identify articles or parameters that could lead us to musculoskeletal infection specialist centers, although the number of true, dedicated centers with multi-disciplinary units at this time remains very low. Medline, Cochrane, and Embase databases were searched, employing the terms: "infected nonunions," "septic nonunions," "specialist's septic centers," "infected nonunion AND hospital" and "infected nonunion AND septic center." After removing papers that did not match our criteria we ended up with 69 articles, which were all observational case series for infected nonunions. Out of those we identified 28 articles (all level IV) that could be used for our analysis. Hospitals with level I trauma centers that had a minimum of two publications about infected nonunions were classified as "specialist centers" (group A) [1–15]. Orthopaedic departments with only one publication were categorized as "non specialized septic centers" (group B) [16–28].

In total, there were 15 publications from 10 centers in group A, and 13 publications from an equal number of centers in group B. Regarding the different treatment methods, in group A, 60% reported using external fixator to stabilize the nonunion, 20% used open reduction and internal fixation (ORIF), 6% intramedullary (IM) nailing and the remaining used more than one technique. In 67% of the patients in group A a bone graft was used, whereas in group B only 38% mention using bone grafting. For the fixation of the bone in group B, in 54% external fixation were applied, 15% used IM nails, 7.7% ORIF, while the rest report the use of more than one technique (external fixators and plates). Most studies do not report the length of hospital stay and time for return to work. In addition, not all of them give data about limb shortening and alignment. The average number of patients in the studies was relatively small. Given also the heterogeneity of anatomical locations of the nonunions among the different studies, valid comparisons are not possible. The number of previous operations was comparable: 2.9 in group A, and 3.1 in group B.

In 54% of group A centers, the infected nonunions were treated in one stage and 46% in two stages. In group B, 73% of the patients were treated in one stage and 27% in two stages. Thirteen studies analyzed the outcomes of treatment with the Ilizarov method, nine studies analyzed the management with a single-stage or two-stage approach and use of cancellous bone grafting, three studies involved vascularized bone grafting, and one study involved a bulk allograft. Follow-up was higher in group A (46.4 months) compared to group B (37.3 months). Both groups demonstrated similar outcomes with respect to the elimination of infection. However, parameters such as length of hospital stay, time to bone healing, time until return to work, functional outcomes and patient reported outcome measures are not available, thus markedly limiting the strength of the recommendation.

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QUESTION 2: Is there a minimum number of complex osteomyelitis procedures a surgeon should perform annually to ensure proper outcomes?

RECOMMENDATION: There is no literature supporting a minimum number of complex osteomyelitis procedures a surgeon should perform annually to ensure proper outcomes. Higher-volume referral centers, centers of excellence and multidisciplinary teams for the treatment of complex osteomyelitis may result in improved outcomes.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 76%, Disagree: 14%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

In the literature reviewed, there is no evidence to answer the question. Osteomyelitis is a complex pathology, which needs years of follow-up to be able to demonstrate the sustained remission of the disease. Osteomyelitis has multiple etiologies: 19% hematogenous, 47% secondary to a contiguous focus and 34 % due to vascular insufficiency [1]. There is no evidence to establish the optimal duration of treatment and many studies do not present good-quality data and include a small number of patients [1,2]. Therefore, most of the recommendations for the treatment of osteomyelitis is based on expert opinions.

In joint arthroplasty, high-volume centers, multidisciplinary teams and centers of excellence have been shown to improve patient outcomes with respect to the treatment of prosthetic joint infections [3]. In trauma, there have been few studies looking at the benefit of high-volume centers for the treatment of complex osteomyelitis and septic nonunions. Bauer et al. retrospectively evaluated the results of a French referral center for complex bone infections. They had 55 patients over the course of 10 years who were treated for infected non-unions of the tibia or femur. They showed that 89% of patients with an infected tibial or femoral non-union treated by a team specialized in complex bone and joint infections using a standardized surgical protocol had bone union and healing of the infection in an average of nine months [4]. In a similar study, Bose et al. reported on 67 long bone infected non-unions over 6 years treated by a multidisciplinary team. They found that 59/67 (88%) went on to fracture union and eradication of their infection [5]. Lastly, Salvana et al. treated 82 patients over 7 years with chronic osteomyelitis with an integrated team approach and found successful union and limb salvage in 77 (94%) cases [6]. In these three studies, the centers treated on average 6-12 cases of complex osteomyelitis per year. At this time there is no data supporting a minimum number of cases of complex osteomyelitis a surgeon should perform annually to ensure good results, but having greater experience collectively at an institution or within a dedicated unit would presumably results in the greatest likelihood of a successful outcome in this difficult cohort of patients.

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Authors: Willem-Jan Metsemakers, Jaime A. Leal

QUESTION 3: Who are the essential members of the multidisciplinary team required to manage infected fractures and non-unions?

RECOMMENDATION: The essential members of the multidisciplinary team managing infected fractures and non-unions require expertise in bone reconstruction, soft tissue reconstruction, microbiology, antibiotic treatment and advanced imaging. It is important to note that the exact members of the group and other specialists required will eventually depend on patient needs and local preferences.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is increasing evidence that teamwork and collaboration among healthcare workers are essential to improving patient outcomes [1,2]. Therefore, it is important to implement a multidisciplinary approach in treatment algorithms of fracture-related infec-

tions (FRI). The use of an antibiotic stewardship program is already a well-known concept for the management of different infection-related entities. These are defined as coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting selection of the optimal regimen, including dosing, duration of therapy and route of administration [3]. With its multidisciplinary approach, an antibiotic stewardship program improves patient safety and outcomes, and when combined with reduced readmission rates, reduces healthcare costs without compromising the quality of care [4–6]. Rodriguez et al. evaluated an evidence-based protocol for antibiotic prophylaxis in open fractures [7]. They demonstrated a short course of narrow-spectrum antibiotics (avoiding the use of broad-spectrum aminoglycosides and glycopeptides) does not increase the risk of soft tissue and skin infections after an open fracture.

Following the Infectious Diseases Society of America guidelines, infectious disease (ID) physicians and clinical pharmacists are the core members of antibiotic stewardship programs, but microbiologists and the implementation of administrative and information technology can also be of great importance [8]. However, as recently stated by Pulcini et al. [9], the composition of these teams is flexible and should be based on existing international recommendations and adapted to the local context based on resources available. Regarding the multidisciplinary approach to FRI, the treatment is based on two pillars: surgical management and clinical management.

Where the surgical management plays an important role, it seems imperative that surgeons (including musculoskeletal trauma surgeons and plastic surgeons) act as central members. Nevertheless, studies within this field are scarce. A multidisciplinary approach, which is constituted of collaboration between musculoskeletal trauma surgeons, the hospital's infection control department, nurses and anesthesiologists as primary team members, has been described to guide FRI prevention strategies [8].

With respect to treatment of FRI, a recent systematic review by Bezstarosti et al. (unpublished data) showed that out of the 93 included studies conducted between 1990 and 2017, only 12 studies (13%) discussed the members that were involved in their multidisciplinary team, with a wide variety of team members available: musculoskeletal trauma surgeons (10 studies), plastic surgeons (5 studies), ID physicians (5 studies), pharmacists (1 study), radiologists (1 study) and not further specified members (3 studies) [10–21]. A study by Bose et al. [12] obtained good results with a multidisciplinary team comprised of orthopaedic surgeons, plastic surgeons, radiologists and ID physicians for treating patients with infected nonunions of long bones [12]. It is important to note that most of the above-mentioned treatment studies focused on chronic/late FRI patients. A study by Dudareva et al. [22] reported a multidisciplinary approach allowed for successful treatment in the majority of cases with osteomyelitis of pelvic bones. The team members in this study were comprised of orthopaedic surgeons, plastic surgeons, and ID physicians. The team was completed by the contribution of specialized nurses, physiotherapists, occupational therapists and musculoskeletal radiologists.

In conclusion, although data specifically focusing on FRI is scarce, a collaboration of different specialties most likely would improve the outcomes in this difficult patient population. No study has evaluated the specific essential participants, but do mention the results with involved members. Antibiotic stewardship programs have already proven their use by means of a multidisciplinary collaboration between ID specialists, clinical pharmacists and microbiologists. The same approach should be applied to set up a main treatment plan for the FRI patient, including surgical, antibiotic and clinical aspects.

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3.3. TREATMENT: RISK FACTORS

Authors: Paddy Kenny, Giedrius Kvederas, John Gibbons

QUESTION 1: What are predictors of the need for allogeneic blood transfusion (ABT) in periprosthetic fractures?

RECOMMENDATION: Predicting factors for allogeneic blood transfusion are: revision arthroplasty, preoperative anemia, increasing age, higher comorbidity index, lower Body Mass Index (BMI), female gender, longer surgical time and hip surgery.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

There is little data regarding predictors of the need for ABT in periprosthetic fractures. Periprosthetic fracture studies typically include a low number of patients, and conclusions about covariates are often not available. These fractures may be treated by either revision surgery or open reduction and internal fixation (ORIF). General indications for ABT in total joint arthroplasty (TJA) can be identical in the first group.

Slover et al. demonstrated that hip arthroplasty had a significantly higher likelihood of blood transfusion (odds ratio (OR) 1.76, 95% confidence interval (CI), 1.68 to 1.83) than knee arthroplasty. Increasing age (age ≥ 80 years; OR, 2.99, 95% CI, 2.82 to 3.17), Medicaid insurance (OR, 1.36, 95% CI, 1.27 to 1.45), higher comorbidity index (score of ≥ 3, OR, 2.33, 95% CI, 2.22 to 2.45), and females (OR, 1.75, 95% CI, 1.70 to 1.80) all had significantly higher odds of blood transfusion after TJA [1].

Parvizi et al., reported that advanced age, low BMI, simultaneous bilateral arthroplasty and low preoperative hemoglobin were independently associated with increased rates of ABT [2].

In a study by Rasouli et al., one-stage bilateral TJA (OR, 3.30;, 95% CI, 3.24 to 3.37; $p < 0.001$), anemia due to chronic blood loss (OR, 2.69, 95% CI, 2.59 to 2.74, $p < 0.001$), deficiency anemia (OR, 2.59; 95% CI, 2.56-2.62; $p < 0.001$) and increased Charlson comorbidity index (OR, 1.24, 95% CI, 1.23 to 1.24; $p < 0.001$) were independent predictors of allogeneic blood transfusion [3].

In the study by Solon et al., 12 patients with Vancouver B2 periprosthetic fractures around cemented collarless polished tapered (CCPT) stems treated by ORIF alone (median follow-up 67 months) were compared with those of nine patients with a similar fracture treated by revision surgery. All 12 patients with Vancouver B2 femoral fractures around CCPT stems treated by ORIF alone healed and all stems restabilized and remained stable within their original cement mantle. These patients had significantly shorter surgical times ($p = 0.002$) and required fewer units of blood transfusion ($p = 0.008$) than patients in the revision cohort [4].

Saidi et al. evaluated 3 different surgical methods for treating comminuted distal femoral periprosthetic fractures in 23 patients over the age of 70 (average age 80, range 70-90). Reconstruction techniques included seven allograft prosthesis composites (APC), nine revision systems (RSA), and seven distal femur replacements (DFR). Operative time and blood loss were found to be significantly less in RSA and DFR patients compared to the APC patients [5], suggesting that more ABTs are required in complex revisions for periprosthetic fractures [5].

Min et al. retrospectively evaluated the clinical and radiographic outcomes of a series of 21 Vancouver type B1 periprosthetic femur fractures (PPF) treated with minimally invasive plate osteosynthesis (MIPO) and locking compression plate (LCP) between February 2011 and February 2017. The mean duration of follow-up was 33.8 months. They also compared outcomes of these patients to similar patients with 19 Vancouver type B1 fractures treated with ORIF between April 2006 and December 2011. The authors found that operative time was significantly shorter and intraoperative blood loss was significantly less in the MIPO group compared to the ORIF group [6].

Fulkerson et al., showed that percutaneous fixation of PPFs with the Less Invasive Skeletal Stabilization (LISS) plate is an effective although technically demanding method of treatment with minimal blood loss [7]. Thomas et al. also had similar results with the LISS plate [8].

Blood loss was minimal and only two of ten patients needed a blood transfusion with Vancouver type B1 fractures treated with percutaneous cerclage wiring for fracture reduction and maintenance of reduction with MIPO utilizing an LCP [9].

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Author: Arjun Saxena

QUESTION 2: Is acute femoral neck fracture a risk factor for infection in patients undergoing hip arthroplasty?

RECOMMENDATION: There appears to be a higher incidence of infection in patients undergoing arthroplasty for acute femoral neck fracture compared to hip arthroplasty for primary osteoarthritis. The reported rate of infection has a wide range; prospective studies should be performed to determine the true rate of periprosthetic joint infection (PJI) in this subset of patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A study on 58,000 elective, primary total hip arthroplasties (THAs) demonstrated a deep surgical site infection (SSI) rate of 0.2% [1]. There are multiple studies reviewing the outcomes of treatment for femoral neck fractures. Most of the studies are retrospective reviews of small cohorts that are not sufficiently powered to study infection rates. Additionally, many of the studies merge primary hemi or total arthroplasty patients with patients who underwent open reduction and internal fixation, and then subsequently a secondary arthroplasty procedure. While most studies report infection rates, the primary endpoint tends to aim at a controversy in treating these fractures, such as cemented versus cementless, or performing hemiarthroplasty versus total arthroplasty. Infection rates vary from 1.2% to 4% [2–5]. A study on 90-day costs following hemiarthroplasty or THA for treatment of hip fractures demonstrated a 17.7% infection rate, but this was not limited to surgical site infections; urinary tract infections, pneumonias and other infections are included in this percentage [6]. A meta-analysis on outcomes of patients who sustained femoral neck fractures reported a 1.0% SSI rate in patients undergoing THA, 1.7% SSI rate in patients undergoing bipolar hemiarthroplasty and a 2.8% SSI rate in patients undergoing unipolar hemiarthroplasty [7].

A study from the Swedish Hip Arthroplasty compared 10,264 patients who underwent THA for treatment of a subcapital hip fracture with 76,520 patients who underwent THA for other reasons and they reported a 0.5% infection rate in the patients who were treated for fracture [8]. It appears that the rate of infection is higher in patients undergoing arthroplasty surgery for the treatment of acute femoral neck fractures.

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3.4. TREATMENT: PROCEDURE-RELATED

Author: Pedro Caba

QUESTION 1: What is the optimal timing of surgical debridement in open fractures?

RECOMMENDATION: It is not possible to establish a clear cut-off for optimal timing of open fracture surgical debridement after injury. Administration of antibiotic prophylaxis and adequacy of debridement is more important than time to debridement. However, we recommend debridement as soon as the patient and operative conditions are optimal.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Debridement is only one of the main pillars of initial open fracture treatment. Antibiotic therapy and proper fixation are also important variables. It is difficult to separate the effects of the different treatments and actions on the onset of infection and other complications. Most clinical studies demonstrate small differences in the time to debridement between comparison groups, and time cut-offs are arbitrary based on historical papers. The implementation of early antibiotic treatment in open fracture treatment has changed the infection rate. Examining the relationship between timing of surgical debridement and infection risk is crucial in guiding clinical practice, as there is still significant variability among surgeons' preferences. Most of the orthopaedic doctrine in this issue is based on historical papers or retrospective studies.

The cut-off of six hours for initial surgical debridement is based on the 1898 Friedrich study which demonstrated in an animal model that wounds debrided within six hours had no infection. This finding became incorporated into orthopaedic doctrine as the "6-hour rule." Robson supported these findings with a clinical study in 1973. He described a golden hour or inflection point of 5.17 hours after injury, which is the time needed for bacteria to reach a critical level of contamination ($> 10^5$ bacteria per gram of tissue specimen).

The first systematic review examining the relationship between infection and time to debridement was published in 2012 [1]. This review included 3,539 patients from various studies. The analyzed data did not indicate an association between delayed debridement and higher infection rates. Studies published since 2012, including a metanalysis, indicate that the 6-hour rule is not supported by evidence. Prodromidis performed a metanalysis in 2016 on the specific topic of the 6-hour rule in open tibia fractures [2]. This paper examined seven articles (only two prospective) involving 610 patients. The statistical analysis did not find any differences in terms of deep infection or non-union regarding the time to debridement.

One major limitation in this literature is the arbitrary cut-off times in the different studies. In 2014, the results of a large prospective cohort multicentre study involving 797 fractures was published. This study did not demonstrate differences in the early (< 6h), intermediate (6-12h) and late (> 12h) groups. Median time to debridement was 9h 15 min, indicating that most patients were not treated early. Another prospective study published by Srour et al. reported similar results [3]. They studied a cohort of 351 consecutive patients treated in the same facility comparing three different cut-off times (< 6 h, 6-18h and 18-24 h). They concluded that the time to operating room did not affect the development of local infectious complications, provided that the operation was performed within the first 24 hours after arrival.

Recent papers have focused on the impact of delayed debridement on infection rates, with conflicting results. Kumar et al. performed a large retrospective study of 404 patients treated with contemporary treatment. They reported that the rate of infection in open lower extremity fractures increases when debridement is delayed beyond eight hours [7]. For upper extremity injuries, delayed debridement did not result in any increase in infections. Penn-Barwell, in an experimental study on rats [8], demonstrated the timing of antibiotics had a more significant effect than surgical debridement on the onset of acute infection, especially when initation of treatment is delayed beyond six hours. When antibiotics were started at two hours, a delay in surgical treatment from two to six hours significantly increased the risk of development of infection but delays beyond six hours did not result in any increase in infection indicating that very early debridement, within two hours of the injury, could have a positive effect. Hull et al., in a prospective series of 459 patients, studied the relationship between delayed debridement and deep infection [6]. They reported that there is a 3% increased risk of infection for every hour of delay. As baseline infection risk is higher for Type IIIB and IIIC open tibia fractures than for lower grade tibia fractures, the increased risk in this group of fractures is much higher when the debridement is delayed. According to this study, the predicted probability of infection in a high grade contaminated tibia fracture increases from 35% at four hours post-injury to 45%. They recommend urgent debridement at the first reasonable opportunity after injury.

In summary, urgent debridement is essential in the initial treatment of open fractures, but the cut-off time is not known. There is little current evidence supporting the 6-hour rule. There is moderate evidence supporting the proposition that delayed debridement beyond eight hours could have an impact on infectious complications, especially in high-grade open tibia fractures. There is only limited evidence supporting very early debridement (< 2hrs).

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QUESTION 2: What is the recommended volume of irrigating fluid in the emergency department (ED) for open fractures?

RECOMMENDATION: In the ED setting, open fractures should be irrigated sufficiently to remove all visible contamination and debris prior to applying dressings.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 75%, Disagree: 15%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Search Method: A comprehensive literature review was performed to identify all studies on the use of irrigation for the treatment of open fractures in the ED. We searched Ovid Medline, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2018 for published studies. Search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) irrigation in the emergency setting was the intervention. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies without clinical follow-up/infection rates, and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in six papers. After removal of duplicates and screening of titles and abstracts, one article was assessed and reviewed.

RATIONALE

Thorough irrigation is a cornerstone in the treatment of open fractures. It is an important step in decreasing bacterial load and removing foreign bodies. Despite extensive literature in the management of open fractures, there has been very little data on the role of wound irrigation in the ED prior to formal debridement in the operating room. Furthermore, the literature is lacking with regard to the optimal volume of irrigation during formal debridement in the operating room [1].

One study by Basat et al. looked retrospectively at clinical outcomes of patients with open fractures of the hand treated with antibiotics and irrigation in the ED alone without formal irrigation in the operating theater. Irrigation with sterile saline was performed by the orthopaedic surgery resident, until the wound was grossly clean. The volume of irrigation and degree of wound contamination were recorded. Of the 68 open fractures treated, 14.8% developed an infection. They found that volume of irrigation correlated with development of infection, with 70.5% of fractures requiring > 1,000 ml of irrigation. They concluded that in the ED, one should use as much fluid as needed to obtain a grossly clean wound. However, this study clearly has its limitations. The degree of contamination is a highly subjective and confounding variable in the association found between increased irrigation volume and increased infection rate. This study looked at open factures of the hand, which are different from those of the lower extremity and typically have a lower degree of contamination and typically exhibit an improved ability to fight infection. Furthermore, this was a retrospective study without control or comparison groups [2].

In contrast to the ED setting, there have been several studies investigating the amount of irrigation required during formal debridement in the operating theater. However, the recommended volumes of irrigation in theater were always described arbitrarily in several published studies [3–6].

Gustilo et al. described the use of 10-14 liters of irrigation intraoperatively [4,5]. Anglen recommended the use of irrigation bags, which are readily available in three liters, for intraoperative irrigation (three liters for Gustilo type I, six liters for Gustilo type II and nine liters for Gustilo type III) without citing any supporting data [6].

Although several studies have investigated open fracture management, the volume of fluid irrigation utilized in them was based on the same rule of "3, 6 and 9" and none of them addressed the amount of irrigation used in the ED [7–11].

After review of the literature, there has been only one clinical study related to the volume of irrigation for open fractures in the ED and this was limited to open fractures in the hand and fingers. Nevertheless, in the ED setting, irrigation of the wound with enough volume until all grossly visible contamination and debris is removed seems, at the very least, an appropriate amount.

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APPENDIX - SEARCH STRATEGY

Ovid Medline: ((open adj3 fracture*).ab,ti. or "Fractures, Open".sh.) **AND** ((irrigat* or lavage or wash*).ab,ti. or "debridement".sh.) **AND**

((volume or amount or quantity).ab,ti.) **AND** ((emergen* or immediate* or urgen*).ab,ti. or "Emergency Service, Hospital".sh.) **AND** ((infection* or sepsis).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Scopus: ((open w/3 fracture*) AND (irrigat* OR lavage OR wash*) AND (volume OR amount OR quantity) AND (emergen* OR immediate* OR urgen*) AND (infection* or sepsis)) in Title, Abstract, Keywords

CENTRAL: ((open near/3 fracture*) AND (irrigat* OR lavage OR wash*) AND (volume OR amount OR quantity) AND (emergen* OR immediate* OR urgen*) AND (infection* or sepsis)) in Title, Abstract, Keywords

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QUESTION 3: What is the recommended volume and composition of irrigating fluid in the operating room for open fractures and post-traumatic wounds?

RECOMMENDATION: Irrigation in open fractures should be performed with normal saline and gravity flow irrigation. 3-9L is a reasonable volume to use. Bactericidal washes with agents like chlorhexidine or povidone-iodine have not been adequately studied in orthopaedic trauma patients, but basic science studies raise concern that they may damage tissues.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Irrigation is a central tenet in open fracture management, reducing bacterial concentrations and removing foreign materials from traumatic wounds. The goal in these injuries is to reduce the known risks of infection, wound healing problems and nonunion. Irrigation requires a balance between removing contaminants and causing further trauma to tissues or spreading contamination. Questions about irrigation include the ideal volume, fluid composition and pressure of irrigation solutions.

The one identified randomized controlled trial comparing different osmolality irrigating agents of distilled or boiled water and isotonic saline did not have clearly-defined outcome measures or follow-up criteria, but reported a 25.5% overall infection rate without any significant difference between the irrigation solutions [1].

Regarding antiseptic solutions, the majority of data is in animal or cadaveric models. This literature raises concerns about host cell toxicity that could affect wound healing or fracture union when utilizing agents such as ethanol, povidone-iodine, bacitracin solution, chlorhexidine solution, or hydrogen peroxide [2–8]. Additionally, there is some data showing that bacterial count reductions from soap or antiseptic solutions may be temporary and followed by disproportionate rebound at later time points, which has led some authors to recommend saline irrigation [9]. Regarding human clinical data, there is one moderate-quality randomized controlled study comparing bacitracin to castile soap for the irrigation of 458 open fractures in 400 patients. Minimum follow-up was 180 days, with an overall infection rate of 15.3%, a wound complication rate of 6.8% and a nonunion or delayed union rate of 23.9%. They reported similar infection and nonunion rates but increased wound-healing complications in the bacitracin group [10].

Volume

We were unable to identify any studies that specifically compared the volume of irrigation in a controlled manner in open or traumatic wounds. However, most studies used a minimum of 3L of irrigation and increased this amount by 3L per additional Gustilo type (3L for Gustilo type I, 6L for Gustilo type 2, 9L for Gustilo type 3), as in the 400-patient RCT by Anglen et al. [10].

Pressure

Pulsatile lavage theoretically improves dislodgement by cyclically compressing tissues then allowing them to decompress and recoil, freeing bacteria and foreign material. Pulsatile lavage has a proven clinical track record in reducing debris and bacterial counts in traumatic wounds when compared to gravity or bulb syringe irrigation [11–14]. However, basic science studies have raised concerns that pressurized lavage may be detrimental to bone healing and may seed bacteria distant to sites of initial contamination [5,15–18].

In the largest study on wound irrigation in open fractures, the Fluid Lavage of Open Wounds (FLOW) Group conducted an international, 41-center, blinded, randomized controlled trial assigning 2,447 patients with open extremity fractures to irrigation with high (> 20 psi), low (5-10 psi) or very low (1-2 psi) pressure with either castile soap or normal saline [19]. Irrigation for Gustilo type I injuries was 3L and types II and IIIA/B were 6L, with type IIIC injuries excluded from the trial. Of note, this study had the additional benefit of relatively standardized care in the pre-, intra- and post-op settings regarding components such as prophylactic antibiotic type and timing, skin prep solutions, debridement, skeletal stabilization and wound management including closures, dressings and soft tissue coverage. They reported no statistically significant difference between the pressure groups for the primary endpoint of reoperation within 12 months for promotion of wound or bone healing or for a wound infection. This study reported an overall 6.8% infection rate, 3.6% wound complication rate and 6.8% nonunion rate at 12 months.

The overall reoperation rate for infection, wound or bone healing was 13.2%. There was a significantly lower reoperation rate in the saline group than the castile soap group (14.8% vs. 11.6%, hazard ratio 1.32, 95% confidence interval 1.06–1.66, p = 0.01). Neither pressure nor solution composition led to significant difference in the secondary outcomes of non-operatively managed infection, wound-healing problem or bone-healing problem. In the subgroup analyses, there was a trend toward superiority without reaching statistical significance for very low-pressure irrigation in tibial fractures [19].

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QUESTION 4: What is the most appropriate management of early (prior to complete wound healing) infection after fracture fixation with stable fixation?

RECOMMENDATION: The most acceptable treatment strategy for trauma patients with early postoperative infection is to perform proper irrigation and debridement, administer intravenous (IV) followed by oral antibiotic therapy and retain stable hardware in place.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The definition and classification of early infection after isolated fracture fixation (IFF) is a dilemma among orthopaedic trauma surgeons [1–3]. However, the clinical picture of early infection including local (e.g., hematoma, wound discharge and dehiscence, erythema around the incision) and systemic (e.g., fever, lethargy) symptoms are usually diagnostic in most situations. Although it is not clear whether the biofilm formation process during the early postoperative infection period will be stopped or delayed with appropriate treatment, the goal of the treatment at this stage is to control the infection until complete union is achieved at the fracture site. After fracture healing, removal of the implant will help to eradicate the infection. This strategy is different than the typical treatment of a periprosthetic joint infection (PJI) in which the infected implant is replaced in two stages (spacer and then re-implantation of the total joint arthroplasty). The treatment strategy might be different based on the evaluation of the local and systemic clinical picture in each individual case. However, based on the available literature and our experience, it is possible to suggest some general recommendations.

The most significant difference between IFF and PJI is the higher chance of infection control and eradication by removing the implant during or after bone healing is complete for IFF cases. Therefore, especially in early postoperative IFF cases, infection control is the main goal of medical and surgical treatment [4,5]. The treatment options are described as ranging from simple antibiotic suppression to removal of the current implant to multiple stage revisions [4,5]. The most reasonable treatment strategy that is applicable to most cases is performing irrigation and debridement, retaining the stable fixation, and administering IV antibiotic therapy [4–7]. More than one washout or debridement may be necessary to clean the operative site and optimize wound healing [8,9]. Local antibiotic delivery (e.g., bead pouch, calcium sulfate beads) may be helpful. Proper soft-tissue coverage and aggressive debridement are the main principals of the surgical part of the treatment. Early flap coverage is critical if hardware is exposed [10].

The use of negative-pressure wound therapy coupled with continuous instillation of an antibiotic solution containing gentamicin and chymotrypsin has also been shown to facilitate a healthy wound bed for healing while maintaining fracture fixation with or without additional surgery for secondary closure [11]. In patients who are at high risk for wound healing problems, incisional negative-pressure therapy may be helpful following the washout [12,13].

Empiric systemic antibiotic therapy followed by organism susceptibility-based therapy should be started after early irrigation and debridement. Systemic antibiotic therapy can be curative or suppressive [14]. After a period of two weeks, IV antibiotic therapy can be replaced by appropriate oral therapy based on the available culture results [15–17]. It is recommended to continue the oral therapy for an additional four to six weeks to prevent chronic

osteomyelitis and suppress the infection [14,18]. In some situations, one may consider long-term oral suppressive therapy until union is achieved before considering implant removal.

Surgical intervention usually is needed to control the IFF. The main challenge is whether or not to remove any stable implants. Removal of stable internal fixation during the early postoperative period, especially in complex situations, will compromise bone healing. It has been shown in multiple studies that there is a strong correlation between fracture stability and bone healing [19–21]. Theoretically, proper irrigation and debridement in the early stage of the IFF can reduce the bacterial load and lower the speed of biofilm formation, which will also help the fracture consolidation process.

During initial debridement, local delivery of the antibiotic at the fracture site can be implemented by using absorbable or non-absorbable materials. However, there is no strong evidence to support the advantage of using local delivery systems as well as systemic antibiotic therapy. Aminoglycosides and vancomycin are the most commonly used antibiotics for local delivery [22]. Industrial premixed or hand-mixed polymethylmethacrylate bone cements are widely used to deliver antibiotics to the infection site by different techniques including molded beads or coated intramedullary nails [23]. The need for removal and less optimal release of the incorporated antibiotics are the main disadvantages of the antibiotic-loaded cements [24]. Good primary results are reported for resorbable materials such as calcium sulfate [25–28]. However, there is no high-quality study to show the superiority of these materials to the antibiotic -loaded cements in terms of clinical outcomes. Recently, hydrogels were introduced as an attractive and effective delivery vehicle for traumatic wounds with reasonable outcomes, which needs to be validated by further high-quality studies [22,29,30].

Although irrigation, debridement, and retention of the stable fixation device were reported as a successful treatment strategy for early IFF in a few studies, there is no strong evidence to support this treatment protocol, especially in the very early stage (before wound healing). Berkes et al. [6] reported a 71% fracture union rate in 121 patients with early postoperative (within 6 weeks) IFF after treatment with irrigation and debridement, implant retention, and culture-specific antibiotic suppression. Open fractures and the presence of an intramedullary nail were reported as the positive predictors of treatment failure. Rightmire et al. [7] reported a similar rate of bone healing (68%) with the same strategy for treatment of early IFF (within 16 weeks). However, there is no available evidence for the appropriate treatment of the infection in the postoperative period before wound healing occurs (two weeks).

Based on the available evidence and our experience, the most acceptable treatment strategy in trauma patients with early postoperative infection is proper debridement, antibiotic therapy (IV followed by oral) and retention of the stable hardware already in place.

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QUESTION 5: What is the most appropriate management of early (before complete wound healing) infection after fracture fixation with unstable fixation?

RECOMMENDATION: The most appropriate management of early (prior to complete healing) infection after fracture fixation with unstable fixation consists of surgical debridement with removal of fixation implants, fracture stabilization, antibiotic therapy and soft tissue coverage, if needed.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after fracture fixation is a serious complication in orthopaedic trauma surgery, as it may eventually lead to devastating outcomes such as amputation [1]. In contrast with periprosthetic joint infections, literature regarding this condition is still limited considering the number of patients affected [1,2]. Nonetheless, in order to unify the evidence available, major efforts have been made to accurately define "infection after fracture fixation" [3]. The current definition includes a classification according to the onset of symptoms and early infection is considered that which occurs during the first two weeks after the index procedure. [2,4]. For this recommendation, this definition will be maintained.

Several systematic and non-systematic reviews gathered the existing evidence for infection associated with orthopaedic implants. All conclude that antibiotic suppression therapy and surgical debridement with implant retention is a suitable option for the treatment of early infection after fracture fixation when fracture healing has not yet been achieved, but the construct is stable [1,2,4–8]. Therefore, to date, this continues to be the standard of care for early infections. Likewise, the outcomes presented by Trebse et al. [9], Rightmire et al. [10] and Berkes et al. [11] all showed favorable results for this method of management, with success rates ranging from 68% to 92%. However, the quality of evidence of these studies is low.

The question remains whether implant retention is still a viable option for unstable fixation. Metsemakers et al. [2], in their more recent review, suggest that implant exchange or removal should be considered in early infections when intramedullary devices are used, unstable fixation exists or insufficient fracture reduction is present. These recommendations are based on the works by Trampuz et al. [4], Kleber et al. [12] and Rightmare et al. [10]. Moreover, several animal studies have addressed the importance of fracture stability in implant-related infections [13–15]. When fixation is unstable, implant retention is not an option. The existing implants do not provide enough stability at the fracture site, which will impair fracture healing as well as facilitate persistence of infection.

Even though both Rightmire et al. [16] and Berkes et al. [17] performed a multivariate analysis, neither of them reported "unstable fixation" as a predictor of treatment failure [10,11]. The quality of the presented evidence is low and the methodology used might not have been appropriate to conclude that implants must be removed under these conditions.

After performing a systematic search of the literature, no conclusive evidence on the management of early infection with unstable fixation was identified. Therefore, our recommendation is based on clinical experience, established knowledge of implant-related infection [18] and the management of infected non-unions [19,20]. Furthermore, adequate coverage of the fracture site with a well-vascularized soft tissue envelope facilitates both control of infection and fracture healing. Therefore, in the case of soft tissue defects or scarred soft tissues with poor vascularity, a soft tissue reconstructive procedure is usually necessary [21,22].

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QUESTION 6: What is the appropriate timing of conversion to internal fixation (in-fix) following external fixation (ex-fix)? How is this altered by pin site infection?

RECOMMENDATION: Timing of conversion should be based on patient characteristics including concurrent injuries and premorbid health and function, as well as injury features and location. One-stage conversion appears to have similar or even lower infection rates compared to two-stage conversion. In the absence of pin site infection, early conversion is preferred.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

American development of external fixation is credited to Parkhill in 1897 and European development to Lambotte in 1900 [1]. Ex-fix is often used in polytraumatized patients as part of a damage-control orthopaedic approach, in injuries with extensive soft tissue compromise, or when appropriate personnel or resources for in-fix are not readily available [2,3]. It is applicable to periarticular fractures, long bone fractures and articular dislocations, making it an essential component of contemporary orthopaedic traumatology.

Recent literature review using the databases Embase, Scopus, Google Scholar and PubMed was performed with the search terms "internal fixation," "external fixation," "timing" and "conversion" in multiple combinations. Articles were reviewed for relevance and studies were then assessed for quality and assigned a level of evidence.

Following ex-fix, conversion to in-fix can have multiple benefits for patients. A prospective comparison of 39 patients with open lower leg fractures treated with primary ex-fix with randomized conversion to intramedullary nailing (IMN) or to cast immobilization showed significantly shorter mean time to union (26.3 vs. 35.4 weeks), higher overall consolidation rates (94% vs. 64%), and better knee and ankle range of motion (ROM) for IMN [4]. Regarding timing of conversion from external to internal fixation (which includes plate/screw constructs and intramedullary nail constructs), major questions within the field are as follows: (1) Should conversion be performed in one procedure (acute) or in two (staged)? (2) Does time in ex-fix affect outcomes following conversion? (3) Do pin site infections increase the risk of deep infection following in-fix? (4) Does timing of soft tissue coverage affect outcomes following conversion? [2].

Regarding staging, theoretically staged conversion should allow time for pin site granulation and decrease infection rates. Therefore, some authors recommend delayed internal fixation until pin sites heal closed [5]. However, data from level IV studies do not support this. Horst et al. reported on two protocols, one for immediate conversion and one for staged conversion from external to internal fixation. They included local excision of skin-pin interfaces and curettage of soft tissues around pin track sites. For immediate conversion, pin sites were disinfected and covered prior to re-prepping of the surgical field. Pin sites were left covered until all in-fix wounds were closed, and then pin sites were left open with antibacterial dressings. For staged conversion, ex-fix was exchanged for a cast and any required soft tissue coverage was performed prior to in-fix. After institution of this algorithm utilizing the immediate conversion protocol, they observed a decrease in time to conversion (mean 6.8 > 5.0 days), hospital length of stay (mean 25.4 > 16.3 days) and complication rate (21% > 8.3%) [6].

Monni et al. performed a retrospective review of 18 patients (24 limbs) undergoing conversion from external to internal fixation for traumatic bone defects or congenital deformities. Indications for conversion included patient dissatisfaction with ex-fix, pin track sepsis, persistent non-union or refracture. In-fix consisted of IMN or plate and screw constructs. Conversion was performed acutely (19 limbs) or staged (5 limbs). The outcome was considered excellent if patients were full weightbearing, pain free, had a mechanically well-aligned limb and did not need further surgery within the follow-up period. The outcome was considered good if patients required subsequent surgery to achieve union and the outcome was considered poor if an irreversible complication occurred. The acute group had 16 excellent and 1 good outcomes (89.4%), with 2 (10.6%) poor outcomes resulting in amputation, both after acute conversion to IMN for infected tibial nonunion. The delayed group had four (80%) excellent and one (20%) good outcomes. They cautioned against using IMNs in patients with a diagnosis of an actively septic nonunion and reported that conversion to in-fix generally produces good to excellent results [7]. Bandhari et al. found that shorter intervals between ex-fix removal and IMN, for planned or salvage procedures, correlated with reduced infection, but do comment that in level IV studies this may represent confounding [8].

Farrell et al. reported on ex-fix with one-stage conversion to in-fix for nine calcaneus fractures. Ex-fix was applied within 24-48 hours and converted to open reduction and internal fixation (ORIF) through a sinus tarsi approach at an average of 4.8 days from ex-fix. There were no pin tract infections, deep infections or wound healing complications [9]. Natoli et al. reported on 16 complex distal radius fractures, 11 of which were open, and treated with an ex-fix and converted to ORIF at a mean of 8.5 days. One patient developed deep infection, and they did not report a relationship with open fractures, time to conversion of < or > 7 days, or ex-fix pins overlapping the definitive fixation [10]. Shah et al. reported on pilon and tibial plateau fractures treated with ex-fix converted to ORIF excluding cases with evidence of overt pin site infection. They demonstrated a 24% rate of deep

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

femoral cases, especially the periarticular bone defects [16]. These publications [14–16] have promise but are retrospective with only small numbers.

The publications regarding the IM technique have many variations including timing to second stage, the presence of antibiotics in the spacer and the type of fixation used for stage one and two [17]. The important unifying principles are radical debridement of infection, proper installation of the cement spacer overlapping the normal bone ends, waiting for the soft-tissue envelope to heal with normal serologic markers and stable fixation during the interval prior to the second stage [18]. Infection eradication is the most essential element in achieving success. This technique therefore requires a minimum of two surgical procedures. The largest series published to date is by Karger et al. [19] with 84 cases. Fifty percent of the cases were for infection, the average number of operations to achieve union was 6.11, and 57% of the defects were larger than 5 cm. An abnormal soft-tissue envelope needs to be addressed with soft-tissue transfer (adjacent or free) in order to promote good soft-tissue healing and a stable wound bed for the second stage [20,21]. The Masquelet technique holds promise but the surgeon should proceed with caution as several surgical procedures may be needed to achieve the desired result. In theory, any size defect can be treated and there is no prolonged external fixation time as in bone transport. The time to achieve union with this technique appears to be independent of the length of the defect; however, a 2 cm defect and a 15 cm defect both may take as long as 10 months to heal [19]. The recommendation is moderate because of the lack of large prospective series reports in the literature and the number of average surgical procedures needed to achieve success.

Kadhim et al. [1] recently published a systematic review of nonunion with segmental bone defects that included 334 tibiae. The most successful method of reconstruction with respect to bone union and function was circular external fixation combined with internal fixation (either bridge plating or intramedullary nail). This provided a 99.8% success rate with respect to both union and function. Papakostidis et al. [22] also demonstrated in their systematic review that distraction osteogenesis with the Ilizarov method statistically significantly reduced the risk of infection in previously infected defects. They also showed that the risk of refracture following removal of external fixation was higher when tibial defects were larger than 8 cm [22].

Rohilla et al. [23] published a randomized prospective study with 70 patients comparing ring fixators and monolateral fixators for infected tibial defects. They concluded that for defects greater than 6 cm, a ring fixator had superior results [23]. They attributed this finding to the larger numbers of patients in the monolateral group who had residual problems with greater than 6 cm of lengthening such as infection, deformity and shortening. Also, the monolateral group had statistically significantly more problems with deep pin tract infections than the ring fixator group [23].

Many other studies have also documented the success of circular external fixation and bone transport in the tibia. Yin et al. [2] in 2014 reported 66 patients with infected segmental tibial bone defects with an average size of 6.3 cm (range, 3–13 cm). All tibiae were treated with bone transport with circular external fixation and united without recurrence of infection. Fifty-nine patients had excellent/good results according to the ASAMI classification [2]. Docking site bone graft was performed in only six patients. The most common complication was pin tract infection in 40 patients with 38 of the 40 being treated with orally-administered antibiotics and pin care. The mean external fixation index was 1.38 months/cm (range, 1.15–1.58 months/cm). Only two patients had refracture after frame removal, which was treated with reapplication of the external fixator [2]. Peng et al. [24] reported 58 cases of tibial infected nonunion with an average defect of 9.2 cm (range, 6–15 cm) that were treated with bone transport with circular external fixation. Fifty-three patients had excellent/good results using the Paley grade and 36 excellent/good functional results. There were no refractures and only one recurrent infection [24].

Hexapod external fixators have also been used for bone transport using the method of Ilzarov. Napora et al. [25] reported 75 infected segmental bone defects of the tibia (average size, 5.4 cm) treated with a hexapod external fixator. Seventy of 75 patients had eradication of infection and full union. Thirty-two patients required a free flap by plastic surgery, and 36 patients had adjunctive stabilization with either an intramedullary nail or plate fixation at or following removal. Many other articles detail the success of circular external fixation and bone transport in the tibia [26–31].

Another treatment option is acute shortening with lengthening. One paper [32] with a total of 42 patients reported similar results when comparing acute shortening with lengthening to bone transport. The only difference was a statistically significantly smaller number of major and minor complications per patient. This technique is helpful only when the fibula is broken and the soft-tissue envelope is amenable to shortening using a transverse incision. Excessive shortening greater than 4 cm can lead to ischemia of the leg due to arterial kinking and the authors highlight the need to monitor the vascular status of the limb whenever shortening is employed.

Some literature has been published on the IM or Masquelet technique for infected tibial segmental bone defects. There is some variability with respect to the technique among the papers, and some critical differences may lead to poorer outcomes using the technique. Tong et al. [16] compared the Masquelet technique for infected segmental tibial bone defects to Ilizarov bone transport. The average bone defect size was 6.8 cm (range, 2.7–15.7 cm). Twenty-six patients had tibial defects with 13 patients in each group. The IM group was treated with external fixation for stage two as well. In this series, there was no statistically significant difference between bone results in the 13 bone transport cases and 13 IM cases. It is interesting to note, however, that a recurrent infection in the IM group was treated with bone transport to union. Functional results were better in the IM group because of the statistically significantly smaller external fixation time (10.2 months [range, 8–14 months] versus 17.2 months [range, 11–24 months]). Seventeen excellent/good functional results were observed for the Masquelet technique versus nine excellent/good functional results for bone transport.

Karger et al. [19] in 2012 published the largest series of the IM technique for segmental bone defects. They included a total of 84 cases that included 61 tibial defects. Of the 61 tibial cases, there was an average time to union of 14.6 months with an average of 11.5 interventions. Full weight bearing was started at a mean of 17.4 months after the initial treatment of the bone defect. Eight tibial cases failed, and six required amputation. Qiu et al. [20] reported 40 tibial posttraumatic osteomyelitis defects. There were 2 groups: a cement bead group (18 patients) and a cement-spacer group (22 patients). The volumes of the bone defects for each group were 32.4 cm^3 (range, 15–40 cm^3) and 40.4 cm^3 (range, 20–70 cm^3), respectively. Nineteen of these bone voids were partial defects. The bone healing time was 8.5 months in the spacer group and 7.5 months in the bead group. Infection control was also similar in the two groups: 88.9% for the bead and 90.9% for the spacer groups. Eighteen patients had soft-tissue coverage by plastic surgery. Stable fixation was obtained at the initial débridement with either internal or external fixation and there were no amputations [20]. This study demonstrates that the IM technique can be successful for small defects.

Sadek et al. [33] also demonstrated that the IM technique for tibial defects smaller than 6 cm was comparable to Ilizarov bone transport in a small, case-matched series totaling 30 patients (14 and 16 patients per group). Giannoudis et al. [34] reported 43 long bones

that were treated with the IM technique; however, only 11 were tibial defects with an average defect size of 4 cm (range, 2–7.5 cm). All bones united with one complication of recurrent infection treated with repeat debridement. This study highlights one of the problems with the IM technique papers in that many different anatomic regions are considered together. Morelli et al. [35] performed a systematic review of the IM technique with 17 papers that met the inclusion criteria; however, only 10 of these papers reported individual patient data for a total of 137 cases. Persistent infection or nonunion was present in 18% of cases requiring repeat surgical interventions. There has been much enthusiasm for this technique because it is technically less challenging for the surgeon and it appeals to patients because it does not have prolonged external fixation time. This technique, however, has pitfalls with many variations of the technique being reported with variable outcomes. Surgeons should proceed with caution as recurrent infection and nonunion may require repeat operations and ultimately increase total treatment time.

Now turning attention to the upper extremity, Adani et al. [36] published a series of 13 cases of VFBG for humeral segmental defects, of which 8 were infected. The average defect in these cases was 12.3 cm (range, 10–16 cm). Five of eight patients required additional procedures (e.g., bone grafting, plate revision, new VFBG). The repeat VFBG was secondary to a vascular pedicle failure. According to Tang criteria, functional recovery was excellent/good in all eight cases and radiographically excellent/good results were seen in five of eight cases.

One series in the literature has 12 pediatric patients with humeral osteomyelitis with an average defect size of 5.5 cm [37]. Initial treatment consisted of excision of infected bone, autograft nonvascularized fibular strut and plate fixation, and limb shortening. Ten of 12 patients healed after the initial surgery. One patient required additional bone grafting. One patient developed a recurrent infection and required re-debridement and re-bone grafting with ultimate success. The average residual shortening of the limb was 3.5 cm (range, 2–6 cm).

Rafiq Barawi [37] published the results of 10 patients with infected humeral defects averaging 6 cm (range, 3–9 cm) treated with Ilizarov bone transport. All 10 cases had Paley class excellent/good results radiographically and functionally at latest follow-up, with an average external fixation index of 1.16 months/cm. Liu et al. [38] reported 11 patients with humeral osteomyelitis and segmental defects. The average gap was 1.9 cm (range, 1–2.7 cm) with an average humeral shortening of 5.6 cm (range, 3.5–8.0 cm). The average humeral lengthening was 9.5 cm (range, 5.5–13.4 cm). The average external fixation index was 1.16 months/cm (range, 1–1.35 month/cm). Ten of 11 patients healed, and all patients were eradicated of infection. All patients had excellent/good results. No docking site bone graft was performed in any of the cases. The most common complication was pin tract infection. Two pins were exchanged in two patients for loosening.

Adani et al. [39] published a series of 12 cases using VFBG in the forearm where 10 of the 12 cases had osteomyelitis. The average defect was 8.4 cm (range, 6–13 cm). Two cases required additional bone grafting and both of these cases had a history of osteomyelitis. A third case was considered a failure secondary to thrombosis of the artery of the VFBG. Therefore, 9 of 10 cases of forearm osteomyelitis healed with 2 requiring additional bone graft procedures. The average time to healing was 4.8 months (range, 2.5–8 months). Internal fixation was used for 9 of 10 cases. Seven of nine patients had excellent/good results clinically and eight of nine patients had excellent/good results radiographically.

The alternative treatment is the IM technique as applied in the forearm. Prasarn et al. [40] published a series of 15 cases of infected forearm nonunion treated with debridement and nonvascularized iliac crest bone graft with open wound healing by secondary intention. All bones united and were free of infection with an average time to union of 13.2 weeks (range, 10–15 weeks). The average defect size was 2.1 cm (range, 1–7 cm). Allende [41] in 2010 published 20 cases with healing of infection and nonunion at an average of 5 months. Luo et al. [42] published a series of 7 forearm infections with an average defect size of 5.8 cm (range, 4–8 cm) treated with the IM technique. The average number of procedures to achieve success in these patients was 3.43 (range, 2–5 procedures). The authors emphasize that a number of debridements may be required to achieve an uninfected environment. Serial debridement's were also determined by Masquelet [18] to be critical to achieve an uninfected wound bed and ultimate success with the technique. One patient required repeat bone grafting [42]. At latest follow-up averaging 86.7 months (range, 41–150 months), all patients were healed, uninfected and had statistically significant improvement in functional scores.

Two studies reported the results of bone transport in forearm nonunions. Zhang et al. [43] published a series of 16 cases with an average defect of 3.8 cm (range, 2.2–7.5 cm) with a mean external fixation index of 1.6 months/cm (range, 1.14–2.0 months/cm). All patients healed, and there was no recurrence of infection. No docking site was bone grafted. Liu et al. [44] reported on 21 patients with infected forearm nonunion who underwent treatment with monolateral fixation. The average defect was 3.1 cm (range, 1.8–4.6 cm), and the external fixation index was 1.4 months/cm. Four patients had docking site bone grafting. Three patients had regenerate bone grafting, and 3 patients had recurrent infection requiring repeat debridement. Mean follow-up was 77.5 months. All forearms healed and were free of infection.

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QUESTION 9: What is the optimum waiting time for bone grafting in staged management of septic nonunion?

RECOMMENDATION: The interval between the first and second stages should be dependent upon infection control and the status of the local soft tissue of the individual patient, rather than any specific time. Therefore, the precise time is unknown. The current recommendations are that if conditions are favorable, the second stage can be performed between 6 and 12 weeks after the first stage. This recommendation may not apply to the Masquelet technique.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Successful treatment of infected long bone nonunions remains a great challenge for the orthopaedic trauma and limb reconstruction surgeon. They are frequently associated with bone and soft tissue loss, failed internal fixation, broken implants, poor vascularity, drainage from sinuses, osteopenia, osteomyelitis, adjacent joint stiffness, deformities, length discrepancies, prior surgery and polymicrobial infection with resistant organisms [1–4]. Available evidence on the operative management of infected long bone nonunions indicates that staged reconstruction (incorporating debridement, antibiotic beads, soft tissue coverage and provisional stabilization, followed by delayed osseous reconstruction and definitive stabilization [3–6]) can achieve union in 93–100% of cases. With expert care under staged protocols by surgeons specializing in musculoskeletal sepsis, persistence of infection is present in only 2-9% of cases [5,6],

TABLE 1. Studies before 2000

Author	Year	Type of Study	Number of Patients	N Septic Nonunion	Mean Follow-up, Months (Range)	Location	Timing of Bone Grafting (Weeks)	Recurrence of Infection	Union
Green [10]	1983	Case series, retrospective	15	15	42 (24-78)	Tibia, femur, ulna	**4**	0%	87%
Esterhai [11]	1990	Case series, retrospective	42	36	Not specified	Tibia	**1**	31%	72%
Ueng [12]	1994	Case series, retrospective	13	8	37 (24-54)	Tibia	**2-4**	0%	100%
Patzakis [13]	1995	Case series, retrospective	32	32	28 (12-49)	Tibia	**8**	0%	91%
Emani [14]	1995	Case series, retrospective	37	37	24	Tibia	**2.1**	0%	100%
Cove [15]	1997	Case series, retrospective	44	12	28 (24-108)	Femur	**Min 2**	0%	92%
Chen [16]	1997	Case series, retrospective	14	14	73 (29-108)	Humerus	**6**	0%	93%
Ueng [17]	1999	Case series, retrospective	15	11	58 (40-76)	Femur	**2-6**	18%	100%

which is significantly better that one-stage strategies or two-stage strategies without local antibiotic depots using polymethyl methacrylate (PMMA) beads [2–4].

Although bone grafting is widely used for the treatment of infected nonunions, there is little evidence on the optimum timing of its use in the staged management of septic nonunion. A search in the Ovid Database (including Embase and Medline) did not identify any studies focusing on the optimum timing of bone grafting. The current evidence is based on studies that report outcomes on the management of infected nonunions. The most commonly reported prerequisite for bone grafting is complete eradication of infection. This is confirmed either clinically (absence of systemic signs such as fever or local signs such as dry healed wounds), by laboratory tests (normalization of inflammatory markers) [7,8] or by biopsies [9].

There has been only one randomized control study on the management of infected nonunion [8]. This study compared the use of antibiotic-impregnated autologous cancellous bone graft with pure autologous cancellous bone graft in the management of infected nonunions. The timing of bone grafting depended on whether muscle transfer was required. Bone grafting was performed after five weeks on average (range two to seven weeks) from the last debridement and application of PMMA if muscle transfer was not required and on an average 10 weeks (range 8 to 12 weeks) if muscle transfer was required. There were no results reported specifically for the two groups with different timing of bone grafting. This study showed that antibiotic-impregnated bone graft was associated with lower rates of recurrent infections than pure bone graft. The rest of the published studies were case-series reporting outcomes on the staged management of infected nonunions.

Interestingly, there has been a change in the timing of bone grafting for the staged management of infected nonunions over the course of the past several decades. Prior to 2000, the mean time of bone grafting was four weeks following the first-stage procedure [10–17] (Table 1). Furthermore, in only two [13,16] out of the eight published studies, bone grafting was carried out later than four weeks from the first-stage procedure. On the contrary, after 2000 the mean time between the first and second stages was 7.9 weeks and in no study was bone graft implanted earlier than four weeks from the first stage [7–9,18–35] (Table 2). This could be partially explained by increasing popularity of the induced membrane technique. The most recent case series use the principles of this technique for the effective eradication of infection and reconstruction of bone defects. The time interval between the two stages of the procedure is essential not only for the eradication of the infection but also for the maturation of the induced membrane. This may be another reason towards the shift of longer waiting times between the two stages.

In summary, even though there are no studies assessing the optimum timing of bone grafting in the management of septic nonunion, current case series recommend an interval of 7-8 weeks while most studies range between 6-12 weeks following debridement.

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TABLE 2. Studies after 2000

Author	Year	Type of Study	Number of Patients	N Septic Nonunion	Follow-up	Location	Timing of Bone Grafting (Weeks)	Recurrence of Infection	Union
Chan [8]	2000	Randomized, prospective	96	96	57 (48-72)	Tibia	**5 or 10**	11%	99%
Tulner [18]	2004	Case series, retrospective	47	22	94 (24-163)	Tibia	**4-7**	18%	95%
Chen [19]	2005	Case series, retrospective	18	18	48 (24-74)	Tibia	**6 or 11**	0%	72%
Jain [20]	2005	Case series, retrospective	42	18	Not specified	Femur, tibia, humerus, forearm	**6**	6%	100%
Babhulkar [21]	2005	Case series, retrospective	113	14	40 (24-180)	Tibia, femur, humerus, forearm	**6-8**	0%	100%
Schöttle [22]	2005	Case series, retrospective	6	6	36 (18-60)	Tibia	**15**	0%	83%
Chiang [23]	2006	Case series, retrospective	12	7	31 (24-37)	Tibia	**Min 13.5**	14%	86%
Ryzewicz [36]	2009	Comparative, retrospective	44	14	Not specified	Tibia	**6**	21%	93%
Stafford [24]	2010	Case series, retrospective	27	7	12	Tibia, femur	**6-8**	14%	57%
Allende [7]	2010	Comparative, retrospective	20	13	18 (10-96)	umerus, forearm	**8.5**	0%	100%
Schröter [25]	2015	Case series, retrospective	18	18	70 (24-96)	Femur	**Min 6**	0%	83%
Scholz [26]	2015	Case series, retrospective	13	13	13 (9-24)	Tibia, femur, fibula, radius, metatarsal	**9.8**	0%	100%
Olesen [27]	2015	Case series, retrospective	8	2	Min 9	Tibia, femur	**7**	0%	50%
El-Alfy [28]	2015	Case series, prospective	17	12	23 (14-38)	Tibia, femur	**11.3**	8%	92%
Mauffrey [9]	2016	Case series, retrospective	12	12	14-23	Tibia	**6-8**	0%	unknown
Canavese [29]	2016	Case series, retrospective	5	4	39 (24-60)	Femur, humerus	**4**	0%	100%
Davis [30]	2016	Case series, retrospective	9	7	42 (18-137)	Forearm	**6-12**	0%	100%
Giannoudis [31]	2016	Case series, retrospective	43	21	Min 12	Tibia, femur, humerus, metatarsal, forearm	**6-8**	5%	95%
Pollon [32]	2016	Case series, retrospective	16	3	78 (12-160)	Humerus	**8.6**	0%	67%
Gupta [33]	2016	Case series, retrospective	9	8	21.5	Tibia	**4-6**	25%	75%
Wang [34]	2016	Case series, retrospective	32	32	27 (24-32)	Tibia, femur	**8.9**	0%	100%
Mühlhäusser [35]	2017	Case series, retrospective	8	3	Min 12	Tibia	**8.7**	0%	100%

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3.5. TREATMENT: MANAGEMENT OF HARDWARE

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QUESTION 1: When should hardware be removed when treating surgical site infection (SSI) in orthopaedic trauma?

RECOMMENDATION: The decision to retain or remove hardware differs by clinical scenario and must take into account extent of the infection and stability of the hardware and fracture.

A methodical approach that addresses the pathogen, host factors and bony and soft tissue deficiencies is required, and includes thorough debridement, dead-space management and soft tissue and bony reconstruction using the established principles of the reconstruction ladder.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Acute or Subacute Infection with Stable Hardware and Fixation

When dealing with orthopaedic implant-related infections, the most common recommendation of nonsurgical consultants is to remove all hardware, obtain deep cultures and administer antibiotics. This is unfortunately only partially correct. Cultures are helpful, and antibiotics are essential, but the removal of stable, functioning hardware in the setting of an acutely infected fracture

should generally be resisted. Although it is well-known that the presence of inanimate material surfaces increases the risk of infection, lowers the inoculum necessary to cause infection and reduces the chances of successful treatment, longstanding clinical experience has demonstrated that skeletal stability reduces the infection rate [2,3]. This reduction is supported by the results of animal studies [4,5]. The mechanism by which instability promotes infection is not clear, but may have to do with interference with revascularization of injured tissues, ongoing tissue damage, altered fluid-flow behavior locally or increased micro-dead space. Although instability seems to interfere with the resolution of infection, the presence of infection does not necessarily prohibit bone healing. A logical strategy is to maintain stable internal fixation, which will facilitate union, and plan for hardware removal later if infection persists after the bone is healed.

For the treatment of acutely infected fractures, Berkes et al. reported a 72% rate of fracture union and resolution of infection utilizing a standardized protocol of operative debridement, retention of *stable* fracture hardware and culture-specific intravenous antibiotics. Factors that were predictors of treatment failure included the injury being an open fracture ($p = 0.03$), the presence of an intramedullary nail ($p = 0.01$), a high association with smoking and any infection with Pseudomonas species or other gram-negative organisms [6].

Other authors have also identified factors that contribute to the successful salvage of acutely infected fractures. These include the maintenance of stable hardware and time of surgery to infection diagnosis less than two weeks [7].

Another factor for successful salvage is the ability to achieve a thorough debridement of the fracture construct. If a collection of pus exists around an implant or under a flap or incision, it must be thoroughly drained. Incisions made for irrigation and debridement of infection should rarely be closed and should be placed carefully to avoid exposing hardware, bone, tendon or neurovascular structures. If these are unavoidably exposed, consideration should be given to flap coverage of the wound. The ability to achieve competent wound closure is another predictor of successful salvage. Vacuum-assisted closure (VAC, (Kinetic Concepts, Inc.)) dressing can be used temporarily in the short-term while awaiting definitive coverage.

As mentioned previously, culture specific antibiotic treatment should be standard when treating acutely infected stably fixed fractures. Furthermore, consideration to adding rifampin to culture proven Staphylococcal infections should be strongly considered. A randomized controlled trial to evaluate the utility of adding rifampin to Staphylococcal infection associated with stable orthopaedic implants demonstrated a 100% cure rate in the group treated with ciprofloxacin-rifampin compared to the 58% cure rate in the group receiving ciprofloxacin-placebo [8]. All patients underwent an initial debridement followed by a two-week course of an intravenous antibiotic regimen of flucloxacillin or vancomycin with rifampin or placebo. Long-term therapy was either ciprofloxacin-rifampin or ciprofloxacin-placebo.

In a study by Rightmire, et al. [9] outcomes in patients with acute infections after fracture repair managed with retained hardware were reviewed. They evaluated the effectiveness of irrigation, debridement and antibiotic suppression in the setting of retained hardware. A successful outcome was defined as a patient obtaining fracture union with the original hardware in place. A failure was defined as a patient requiring hardware removal before fracture union [9]. There was only 68% success with an average of 120 days until fracture healing, and 36% of these patients went on to present with reinfection. The majority of the infected fractures that failed debridement and antibiotics with retained hardware failed within three months.

It is important to consider all information when deciding to retain or remove hardware in treatment of these infections, including the specific characteristics of the fracture, the type of fixation, the virulence of the pathogen and physiology and function of the patient.

Acute or Subacute Infection with Unstable Fracture, Fixation and/or Hardware

The presence of excessive motion, the displacement of hardware on radiographs or the visualization of radiolucencies around screws, rods or fixator pins denotes an unstable situation. This instability compromises the ability to overcome infection and to heal the fracture. Bacteria that are attached to surfaces such as metallic fixation devices or dead bone become resistant to the action of antibiotics through the production of biofilm. In the face of unstable hardware or fracture malalignment, the hardware should be removed.

Animal studies with an infected fracture model document the detrimental effects of fracture instability. The infection rates at two weeks post-infection were lower in internally-fixed fractures with stable fixation compared to unstable fractures with loose pins. Stability lowers the incidence of *S. aureus* infection and other gram-positive organisms. However, gram-negative infections were less likely to be successfully suppressed in the internally fixed group and the infection could only be eradicated if the hardware was removed [5].

Friedrich et al. noted similar findings in infected fractures with retained hardware [4] and infection developed in 45% of unstable fractures. However, infection did NOT occur after rigid fixation. With rigid fixation, no significant difference in the time to bony union was noted between the infected versus uninfected fractures. It is important to note that fracture instability, particularly with loss of fixation, may also be a confounded clinical scenario, demonstrating a more widespread infection that prevents callus formation and leads to bone loss and loss of fixation.

Chronic Osteomyelitis

Debridement

Chronic infection after injury is largely a surgical disease and is rarely successfully treated by antibiotics alone. Surgical debridement should be undertaken by experienced surgeons using particular techniques that adhere to established principles, many originally described by Cierny [10–14]. If infection persists after fracture union, hardware must be removed and avascular bone and soft tissue debrided. In general, previous incisions should be used, and all necrotic soft tissue should be removed [10–14]. In the case of structures important to function and with questionable viability (tendons and ligaments), a staged approach can be taken. Care should be taken to not strip viable periosteum from bone. Sclerotic or sequestered bone should be removed until all the remaining bone appears healthy and bleeds well. A high-speed burr is a gentle way to accomplish removal of necrotic infected bone [10–14].

Local Antibiotic Delivery

To prepare defects for grafting or coverage following debridement, antibiotic-impregnated polymethyl methacrylate (PMMA) beads, rods or blocks are often placed to deliver a high concentration of antibiotics locally while avoiding systemic toxicity. Antibiotic elutes from the PMMA by diffusion from the surface. Although most of the drug elutes in the first 24 hours, therapeutic levels of drugs have been detected in some cases for as long as 90 days. Tissue concentrations may be higher and persist longer than those seen in

elution experiments. Although many surgeons believe that antibiotic beads used to treat osteomyelitis should be removed, one retrospective study suggested that improved outcomes followed leaving the beads in situ [14].

After removal of an intramedullary rod, placement of antibiotic beads offers no mechanical support. Beads within the intramedullary canal must be removed within 10 to 14 days or subsequent removal may be extremely difficult [15,16]. Antibiotic cement rods can be custom-made at the time of surgery using varying chest tubes as molds [16]. Following thorough medullary canal debridement, the antibiotic rod is inserted and does provide some mechanical stability**.** If additional debridements are necessary, the antibiotic rod is exchanged. At the time of definitive closure, the antibiotic rod is left intact in the canal, and the wound is closed directly over it. After a six- to eight-week interval, the rod can be removed and bony reconstruction can be undertaken.

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QUESTION 2: Which surgical treatment (plate, nail or external fixator) for open tibial shaft fractures results in lower rate of infection?

RECOMMENDATION: There is little to no difference in terms of infection rates for Gustilo-Anderson types I–II treated by either circular external fixator, unreamed intramedullary nail or reamed intramedullary nail. For Gustilo-Anderson IIIA-B fractures, circular external fixation appears to provide the lowest infection rates when compared to all other fixation methods.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review was undertaken on all English language articles on infection rates following the treatment of open tibial shaft fractures. The literature search included Google Scholar and the Medline, Embase and Cochrane databases. The search terms included open tibia, tibia fracture and tibial diaphysis with the Boolean terms 'AND' and 'OR.' All abstracts were reviewed, and the full articles were obtained for all potentially suitable articles.

Review articles and those that included peri-articular open fractures and pediatric fractures were excluded. A total of 54 articles were excluded for review. Information regarding Gustilo-Anderson types and infection rates were extracted from all included articles (Table 1).

Statistical analysis revealed that across all Gustilo-Anderson types, circular external fixation and intramedullary nailing have significantly lower infection rates compared to plate fixation or monolateral external fixation. Across all types, there is minimal to no difference between circular external fixation and unreamed intramedullary nailing or reamed intramedullary nailing (Table 2).

When Gustilo-Anderson type IIIB injuries are isolated, circular external fixation appears to have a significantly lower risk of risk of infection when compared to reamed and undreamed intramedullary nail fixation (Table 4).

In conclusion, from the available published English literature on infections rates for open tibial shaft fractures treated by various different fixation methods, plate fixation and monolateral external fixation have significantly higher infection rates when compared to circular external fixation or intramedullary nailing. There appears to be little to no difference for Gustilo-Anderson types I – IIIA treated by either circular external fixator, unreamed intramedullary nail or reamed intramedullary nail. For Gustilo-Anderson type IIIB fractures, circular external fixation appears to provide the lowest infection rates when compared to all other fixation methods.

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TABLE 1. Summary of infection rates with different fixation methods from the literature review

Fixation	Type	Cases (n)	Infected Cases (n)	%
Plate [1–4]	GA I	49	3	6.1
	GA II	80	7	8.8
	GA IIIA	36	9	25.0
	GA IIIB	34	5	14.7
Monolateral external fixation [1,3–19]	GA I	9	0	0.0
	GA II	76	2	2.6
	GA IIIA	373	41	11.0
	GA IIIB	238	50	21.0
Circular external fixation [17,18,20–28]	GA I	10	0	0.0
	GA II	63	0	0.0
	GA IIIA	145	3	2.1
	GA IIIB	198	6	3.0
Unreamed Nail [1,4,5,7,9–13,16,19,29–51]	GA I	533	6	1.1
	GA II	734	19	2.6
	GA IIIA	554	32	5.8
	GA IIIB	558	102	18.3
Reamed Nail [6,18,21,32,33,38,40,41,48,52–54]	GA I	401	6	1.5
	GA II	493	15	3.0
	GA IIIA	230	5	2.2
	GA IIIB	240	40	16.7

TABLE 2. Infection rate ratio (IRR) differences between all treatment types for all GA types (I, II, IIIA and IIIB)

Treatment	IRR	95% CI	p-value
Circular fixator	Reference		
Plate	5.57	2.73 - 11.38	<0.001
Monolateral fixator	6.17	3.12 - 12.23	<0.001
Unreamed nail	3.10	1.03 - 9.25	0.044
Reamed nail	2.24	0.73 - 6.89	0.161

TABLE 3. Infection rate ratio (IRR) differences between all treatment types for GA types I, II and IIIA

Treatment	IRR	95% CI	p-value
Circular fixator	Reference		
Plate	8.34	2.78 – 25.23	<0.001
Monolateral fixator	6.82	2.57 – 18.12	<0.001
Unreamed nail	2.27	0.74 – 6.96	0.044
Reamed nail	1.68	0.63 – 4.47	0.161

TABLE 4. Chi squared analyses of infection rates of reamed and unreamed nail vs. circular fixators for Type IIIB open fractures

Treatment	OR	95% CI	p-value
Circular fixator	Reference		
Unreamed nail	6.40	2.65 – 15.44	<0.001
Reamed nail	7.19	3.09 – 16.59	<0.001

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QUESTION 3: When performing intramedullary (IM) fixation, what is the evidence regarding reaming versus non-reaming and the association with infection?

RECOMMENDATION: Based on the current evidence, there is no difference in infection rates following IM fixation of long bone fractures using a reamed or non-reamed technique.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Using an IM fixation technique has become the accepted standard in treating long bone fractures. Tibial fractures are the most common type of long bone fracture encountered and therefore are the most studied in the current literature [1,2]. Evidence has supported that IM nailing is superior to external fixation with regards to patient outcomes [3–5]; however, there has not been a consensus with regard to reamed versus non-reamed IM nailing technique.

Classically, the arguments against the use of reaming point to the risk of fat embolization from the marrow-generated from the increased intramedullary pressure created during the technique, and development of acute respiratory distress syndrome (ARDS) [6,7]. Also, long bone fractures are often the result of high-energy injuries and are accompanied with varying degrees of periosteal stripping [4]. This inherent soft tissue damage can predispose patients to complications, such as infections, especially in open fractures. In addition to the soft tissue compromise secondary to the trauma, reaming has also been shown to disrupt endosteal blood flow and to cause thermal necrosis of the bone [4,7]. This is thought to have the potential to further increase the risk of infection due to added insult to the soft tissue [4]. To avoid such adverse effects and complications, a non-reamed IM nailing technique was developed.

Despite the described adverse results of reaming, current literature has not convincingly proven an association between reaming and infection rates. Finkemeier et al. conducted a prospective, randomized study analyzing 94 patients with closed and open tibial fractures treated with either reamed or non-reamed IM nailing [8]. There was no statistically significant difference in the infection rate between the two study groups. When comparing infection rates of only closed fractures treated with reamed and non-reamed techniques (4% vs. 4%, p = 0.945), no statistical difference was observed [8]. Open fractures also had no significant difference in infection rates when treated with the studied techniques (5% reamed vs. 4% non-reamed, p = 0.851) [8]. Similarly, Blachut et al. conducted a prospective study of 141 fractures randomized into reamed and non-reamed groups and found no increased rate of infection [9]. Both of these studies noted that their smaller sample sizes could limit the quality of the evidence they presented [8,9].

A much larger prospective, blinded randomized trial was conducted by the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) investigators [1]. This study randomized 1,319 tibial shaft fractures into reamed or non-reamed cohorts and did not allow re-operations for nonunion to occur before six months in order to effectively evaluate the outcomes of the techniques [1]. The results of their study found a statistical difference in the relative risk (RR) of a primary event when a reamed technique was used in a closed tibial fracture (RR = 0.67 confidence interval (CI), 0.47-0.96, p = 0.03) [1]. The RR of an infection in a closed fracture, however was not statistically significant when comparing the reamed and unreamed groups (RR = 1.37, CI 0.48-3.93, p = 0.56) [1]. The same was seen in open fractures when comparing the infection rates of the two techniques (RR = 1.27, CI 0.67-2.40, p = 0.46) [1]. The SPRINT trial was unable to draw any conclusions about risks of infections between reamed and non-reamed techniques due to disparity between the study groups. The authors of the study noted that there was potential bias in their study, for their surgeons had more expertise with the reamed technique [1]. This could have biased their data against the non-reamed group.

A systematic review and meta-analysis of a pooled group of 646 patients conducted by Bhandari et al. found a RR of reamed versus nonreamed IM nails of 0.98 (CI 0.21-4.76, p = 0.86) for rate of infection [10]. They did note trends in favor of reamed IM nailing with closed fractures and nonreamed IM nails in open fractures. Due to the lack of significance in the results, however, they were unable to draw definitive conclusions pertaining to infection rates between the studied techniques [10]. Foote et al. conducted a network meta-analysis to analyze all treatment options for open tibial shaft fractures [2]. Similar to Bhandari et al., they were unable to find a difference between reamed and non-reamed IM techniques (direct evidence non-reamed vs. reamed odds ratio (OR) = 0.74, CI 0.45-1.24) [2].

A third systematic review was also unable to establish a statistically significant difference between infection rates when using a reamed technique as opposed to a non-reamed technique (RR = 1.19, CI 0.71-2.00) of the 1,545 patients included in this analysis [11]. Of note, the Duan et al. systematic review was heavily dominated by the inclusion of the SPRINT trial which contributed the majority of the patients to the overall analysis and was cited as a potential weakness of their study [11].

Despite concern of an increased rate of infection when a reamed technique is used for IM nailing, current evidence has been unable to elucidate a difference between reamed and non-reamed IM nails in this regard. There are several studies addressing the issue, however smaller sample sizes in all of these studies prevents one from drawing a definitive conclusion [8,9,11]. In addition, the current literature focuses primarily on outcomes aside from infection. The high-energy nature of fractures treated with these techniques as well as the open/closed nature of the injury can also be confounding factors limiting many authors' ability to draw definitive conclusions. Therefore, there is no conclusive evidence linking

IM reaming with increased rates of infection when compared to non-reamed techniques.

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QUESTION 4: Are antibiotic coated rods (ACRs) and antibiotic coated plates (ACPs) an acceptable alternative to cement only implants?

RECOMMENDATION: Antibiotic-loaded polymethyl methacrylate (AL-PMMA) spacers can be considered an established treatment concept for local antibiotic delivery in osteomyelitis and implant-associated infections.

ACRs and ACPs can also be of value in specific indications, mainly infected non-unions, in order to address both local delivery of antibiotics and biomechanically stable fixation of the non-union site to allow for possible spontaneous bone consolidation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Biomechanically stable ACRs, such as antibiotic coated interlocking nails, and ACPs exhibit the advantage of additionally providing sufficient biomechanical stability to allow for bone healing in infected non-unions compared to antibiotic delivery only by biomechanically unstable drug carriers. There are only a few limited case series available on biomechanically stable ACRs [1–4] and ACPs with the study of Conway et al. being the largest with 110 patients on locked ACRs that were retrospectively analyzed [1]. A good overall clinical outcome could be accomplished with an overall limb salvage rate of 95% (105/110 patients) in infected non-union and infected arthrodesis.

For ACPs, there is only one case report and one case series with four patients all of whom showed healing of the formerly infected fracture by the use of the ACPs [5,6].

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QUESTION 5: What is the ideal composition of antibiotic-impregnated intramedullary (IM) nails?

RECOMMENDATION: The ideal composition of antibiotic-impregnated IM nails is unknown. The core should consist of a rigid structure such as an Ender's IM nail, Ilizarov threaded rods, IM locked nails, carbon fiber nails or sectioned pins or guidewires. We recommend at least 2 grams of vancomycin and 2.4 grams of an aminoglycoside be added to each pack (40 grams) of polymethyl methacrylate cement. If a specific micro-organism is isolated, targeted antibiotic therapy should be included.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Infection following IM nailing of long bone fractures is a recognized complication that can be difficult to treat successfully [1]. The incidence is variable depending on the degree of soft tissue and bone compromise, ranging from 1.8% in closed fractures and Gustilo type I open fractures up to 12.5% in type IIIb open fractures [2]. Almost half of these are caused by multiple organisms. Zych et al. [2] reported that 56% of these infections were caused by a single organism, predominantly caused by *Staphylococcus aureus* (50%) followed by *Bacteroides fragilis* (3%) and *Streptococcus pyogenes* (3%). The remaining cases were caused by a combination of these and *Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Escherichia coli,* and *Pseudomona aeruginosa*. In all infections, *Staphylococcus aureus* was present in 64% of cases.

Antibiotic cement-impregnated IM nails (ACIMNs) have been described as a treatment option for this complication. These are designed to provide stability while delivering local antibiotics. Initially described by Paley and Herzenberg in nine cases, they used a chest tube as a mold and a guidewire as a core, covered with antibiotic-loaded bone cement [3]. The treatment strategy with the use of ACIMNs is generally performed in a two-stage fashion. An initial debridement and implantation is followed by subsequent removal with or without definitive hardware exchange [4–6].

The greatest disparity among ACIMNs is the element used as the core. Investigators have reported different components including Ender's IM nails, Ilizarov threaded rods, IM locked nails, interlocked carbon fiber nails, sectioned pins or guidewires [7]. ACIMNs act as antibiotic-loaded cement spacers, similar to those used in two-stage exchange arthroplasty for periprosthetic joint infection treatment, [8] with additional temporary fracture or bone stabilization [9].

Regarding construct rigidity, the core diameter is the most important factor. It is important to note that these are significantly weaker than conventional IM nails given the antibiotic coating. Thus, a balance between the core diameter and planned diameter of ACIMN should be carefully calculated. In a mechanical study by Marmor et al. [10] different core diameters were evaluated. A 5.8-mm-core diameter cement rod bending stiffness was reportedly higher, 4.96 ± 0.67 N/m2, than a 3-mm-core, 3.07 ± 0.28 N/m2, ($p = 0.0039$). The second important factor is the thickness of the cement mantle, which is currently unknown given different variables of the cement composition. Vaishya et al. [11] suggest a cement mantle thickness of 2 to 3 mm without clear evidence supporting this statement. The reduction in the volume of cement coating raises concerns regarding the effectiveness of antibiotic delivery. However, the elution properties of the impregnated antibiotics have been shown to depend on the surface area and porosity of the mixture, not the thickness. In a study by Karek et al. [12], they demonstrated that a thin mantle would potentially allow for higher elution of antibiotics caused possibly by the result of a cooler exothermic reaction.

Different techniques of ACIMN fabrication have been described [3,7,13]. The use of a mold and manual fabrication has been commonplace for the past two decades. These have different advantages and disadvantages such as fabrication speed and the morphology of the implant. Molds such as chest tubes seem to be the best option as they generate a smooth implant that facilitates their later removal. Kim et al. [5] evaluated the time required to peel the chest tube off the ACIIN using different cement-cooling techniques. They found that the fastest and most effective way is cooling the cement in cold water and pre-lubricating the chest tube with mineral oil. They also recommend the use of 3-mm beaded IM guidewire that is cut to a length 3 cm longer than the length of the tube allowing creation of a hook or loop for subsequent removal.

Broad-spectrum antibiotics are routinely used as infections are generally poly-microbial. The most commonly used antibiotics are vancomycin, tobramycin, gentamycin or a mixture of these [14]. Antibiotics must have certain properties in order not to compromise their efficacy. Anagnostakos et al. [15] identified these properties as availability in powder form, wide spectrum coverage, bactericidal activity, high elution properties, thermo-stable and hypoallergenic [16]. Targeted therapy if a micro-organism has been isolated is desired if certain criteria are met.

Reported success rates range with the use of ACIMNs range from 69% to 100% with the use of different constructs and similar antibiotic compositions [4,6,17–21]. We, therefore, consider the ideal composition currently unknown. We do consider, with the available literature descriptions, that there are several considerations that need to be employed in the construction of these devices. The core should consist of a rigid structure with the largest diameter possible to increase rigidity while not compromising cement mantle stability. The system should have an extraction element for subsequent removal. Based on recommended antibiotic concentrations for spacers, most authors use a mixture of at least 2 gm of vancomycin and 2.4 gm of an aminoglycoside in 40 gm of bone cement. Prior research has shown that this is the minimum concentration needed for attaining long-lasting antibiotic elution in the surrounding space [22]. There is little evidence of systemic toxicity with high antibiotic concentrations in the cement mixture used to coat nails, but a dosage safety range has not been established. If a specific micro-organism is isolated, targeted antibiotic therapy should also be considered.

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QUESTION 6: What is the ideal composition of antibiotic impregnated (ABI) spacers/beads in post-traumatic infections? Is preoperative microbial identification necessary?

RECOMMENDATION: There is currently limited evidence with regards to the ideal composition of ABI polymethyl methacrylate (PMMA) spacers or beads in post-traumatic infections and the need for preoperative identification of the causative organism. Available data suggests that PMMA spacers, empirically impregnated with at least 2 gm of vancomycin per 40 mg of PMMA (with or without gentamycin), may result in quiescence of infection in a high percentage of cases with an acceptable associated rate of bony union. Preoperative microbial identification is of unclear utility.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The challenge of achieving adequate local tissue antibiotic concentrations with systemic antibiotics has prompted the addition of local antibiotic therapy in the majority of bone infection protocols. The use of ABI PMMA beads is well established in the treatment of chronic osteomyelitis. Klemm reported a cure rate of over 90% in 405 cases of chronic sequestrating osteomyelitis with the use of gentamycin-impregnated PMMA bead chains [1]. Notably, the beads were pre-manufactured with gentamycin and Klemm found no change in the gentamycin resistance profile over a seven-year period. The use of local antibiotic therapy has also been advocated in the post-traumatic setting. Numerous review articles advocate for the use of ABI PMMA or other forms of local adjuvant antibiotic therapy in the setting of septic non-union or post-traumatic infections [2–5]. Interestingly a recent comparison of the outcomes of treatment with ABI beads versus spacers revealed no difference in the rate of infection control, time to union or complication rate with either configuration [6].

The induced membrane ("Masquelet") technique has gained popularity in the management of post-infective bone defects [7]. The procedure involves the placement of a PMMA spacer in the defect, followed by a subsequent second-stage bone grafting into the resulting induced membrane [8]. Originally the procedure was described using bone cement without antibiotics. Masquelet reasoned that the inclusion of antibiotics may increase the risk of resistance to the offending organisms and that it changed the biological characteristics of the induced membrane [9]. This concern was validated, in an animal model by Nau et al., who demonstrated variations in the nature of the induced membrane with different types of bone cement and supplemental antibiotics [10]. Notably, Palacos[å] with gentamycin still resulted in a positive rate in cell growth. However, in clinical studies involving post-traumatic (not post-infective) bone defects the concerns regarding inhibition of bone healing were not realized, with reported union rates of 82% (in cylindrical defects) to 100% (in conical defects) with the use of ABI spacers [11,12].

While the original technique involved PMMA without antibiotics, several other authors have utilized the potential advantage of local antibiotic elution during the construction of the spacer [13–18]. If the data from the meta-analysis by Morelli et al. is scrutinized it appears that there may well be a therapeutic advantage with the addition of antibiotics in terms of infection control. When evalu-

ating the studies that included only post-infective bone defects it is noteworthy that there was recurrence of infection in two out of 17 cases in which PMMA without antibiotics was used, [19] compared to no recurrence in 58 cases in which ABI spacers were used [5–8]. Furthermore, the addition of antibiotics may not necessarily result in inferior bony healing with union reported in 100% of the cases in which ABI PMMA spacers were used. The heterogeneity of these studies, however, prevents drawing firm conclusions in this regard. The successful use of ABI spacers has, however, recently been corroborated in a larger series (involving 22 cases of acute post-traumatic defects and 21 post-infective defects) by Giannoudis et al., who reported an overall union rate of 93% and only one case of recurrent infection at 2-years follow-up.

Despite the promising results that have been achieved with ABI PMMA, the optimal composition of the spacers remains to be determined. Rathbone et al. examined the effect of 21 different antibiotics on the viability and osteogenic activity of osteoblasts. Amikacin, tobramycin and vancomycin were found to be the least cytotoxic agents [20]. No well-designed comparative clinical studies to asses different spacer compositions have yet been performed in the post-infective setting. The choice of antibiotic appears to be empirical in most studies and none have reported it is necessary to preoperatively determine the causative organism. The most popular composition appears to be 2 to 4 gm of vancomycin added to 40 gm of PMMA with or without gentamycin (or tobramycin) [5,6,10–12].

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QUESTION 7: Should antibiotic cement rods (ACRs) be left permanently in situ?

RECOMMENDATION: If the ACR is used as a temporary non-locked implant for infection control, it should be removed and replaced by a biomechanically stable construct (e.g., locked intramedullary nail). If the ACR is used as a locked implant for both local delivery of antibiotics and provision of stable biomechanical conditions for consolidation of the non-union site, it can be left in place.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 70%, Disagree: 30%, Abstain: 0% (Super Majority, Weak Consensus)

RATIONALE

ACRs can be used for two different indications.

1. ACRs are used as non-locked temporary implants for the local delivery of antibiotics into the intramedullary canal to eradicate the infection. In cases with stable bone conditions, e.g., chronic osteomyelitis in long bones, missing rotational stability of the ACR is not relevant, whereas in infected non-unions with unstable bone conditions, the ACR is removed after infection control and replaced by a biomechanically stable implant, in most cases by a standard interlocking nail in a subsequent revision procedure.

For this indication, only technical notes, case reports and small case series with a maximum of 19 cases in one study exist [1–8]. In the 18-patient case series by Qiang et al., the mean indwelling time of the ACR was 57 days, ranging from 35 to 123 days [6]. Sancineto et al. published 19 cases with removal of the ACR between 6 and 76 weeks after surgery [7]. Badhra and Roberts reported some difficulties in

the removal of antibiotic nails that have been implanted for more than two months. They found that proximal incarceration of the nail requiring debridement of bone could occur and might need to be addressed using osteotomes [1]. Paley and Herzenberg also retained their cement-coated rods for up to 753 days without any major complication except rod fracture in one patient [5].

There is one study by Selhi et al. in which in some cases of unlocked ACRs were used for infected non-unions and these were retained for a longer period of time in order to achieve bone healing despite the absence of rotational stability. ACRs were kept for a period ranging from 6 weeks to 22 months with an average of 10.6 months [8]. These rods were usually retained until bony union occurred or secondary procedures like external fixation, intramedullary nailing, and/or bone grafting was performed.

2. ACRs can also be used as locked ACR with adequate biomechanical stability in infected long bone non-unions for both local delivery of antibiotics and provision of stable biomechanical conditions for consolidation of the non-union site [9–11]. For this indication, several retrospective case series (with a maximum of 110 cases in one study) exist. Good clinical outcomes with a healed uninfected bone in 105/110 patients (95%) was demonstrated [9]. Removal of the ACR was not reported in the articles and one can assume that the implants were left in place in order to not weaken the bone.

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3.6. TREATMENT: WOUND COVERAGE

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QUESTION 1: Is there evidence to support one type of flap coverage over another (e.g., muscle over fasciocutaneous flap) after open tibial fractures?

RECOMMENDATION: Different types of flap coverage after open tibial fractures have essentially equivalent and comparable outcomes in terms of flap survival, bone healing, stress fracture, infection, chronic osteomyelitis and donor site morbidity. Local flaps should be considered in low energy trauma, when available. The type of flap should be tailored based on the extent and the depth of the soft tissue defect and the location of the fracture. In high energy fractures of the tibia, muscle flaps may offer a more reliable reconstruction with fewer flap failures and fewer reoperation rates.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Multidisciplinary management of severe open tibial fractures with radical debridement, skeletal fixation and early stable coverage is essential for infection prevention and high-quality, cost-efficient trauma care [1]. The Gustilo-Andersen grading system of open tibial fractures is a significant prognostic factor of infectious complications and non-unions [2]. Open fractures of the tibia have a high incidence of infection and malunion [3,4]. Wound coverage does not only prevent wound desiccation and infection, but also contributes to fracture repair by serving as a local source of stem or osteoprogenitor cells, growth factors and vascular supply [5,6].

There is a growing body of evidence demonstrating that the biological characteristics of the tissues in a flap can significantly influence fracture healing, and the rate of delayed union or non-union. Timing of soft tissue coverage is also a critical determinant of the length of in-hospital stay and most of the early postoperative complications and outcomes [7]. Early coverage has been associated with higher union rates and lower complication and infection rates compared to those reconstructed after 5-7 days [2,5,7–9]. Furthermore, early reconstruction improves flap survival, as microsurgical free flap integration becomes more challenging with a delay due to an increased pro-thrombotic environment, tissue edema and the increasingly friable vessels. Only those patients presenting to facilities with an actual dedicated ortho-plastic trauma service are likely to receive definitive treatment of a severe open tibia fracture with tissue loss within the established parameters of good practice [7]. "Fix and flap" is being recommended for specialist hospitals where the expertise is available. Antibiotic bead pouches to decrease infection rates have been advocated when there is segmental tissue loss,

gross contamination or established infection as pre-flap tissue infection seems to be an independent predictor of adverse flap and skeletal reconstruction outcomes [10,11].

Fasciocutaneous flaps may be better suited and superior compared to muscle flaps for coverage of the shallow defects at the rapidly uniting metaphyseal fractures around the ankle, particularly with no massive bone or soft tissue loss [6,10,12]. They are easier to monitor postoperatively and tend to have better venous and lymphatic drainage with less acute swelling and better aesthetic appearance [10,13]. Additionally, they become potentially sensate and pedicle-independent from secondary neuro-angiogenesis permitting low-risk flap elevation for subsequent procedures [10,14,15].

Human stromal cells derived from muscle exhibit a significantly greater potential for osteogenesis than those from fasciocutaneous tissue, including both skin and adipose tissue, and are equivalent to those from bone marrow [2,16,17]. Muscle flaps covered with skin grafts in direct apposition with diaphyseal fractures help to obliterate the dead space, reducing potential complications associated with hematoma formation. They may be superior in eliminating bacteria from the wound bed [5] and enhancing healing, but remain pedicle-dependent and difficult to elevate for secondary procedures such as bone grafting. Muscle-only flaps may also have a false high rate of re-operation due to difficult postoperative monitoring. An alternative with the biological benefits of both is a chimeric flap, such as the free anterolateral thigh flap, which includes a segment of *vastus lateralis* [11,14]. Muscle flaps with a cutaneous skin paddle are easier to monitor and thus have a higher salvage rate. Rotational flaps with fasciocutaneous tissue and muscle for proximal defects have shown significantly more complications including infection, necrosis or partial flap loss, compared to free muscle flaps in patients with the most severe grade of osseous injury (44% compared to 23%), and are more likely to require operative re-intervention [6,18].

The selection of proper free flaps for the appropriate defects is also of critical importance, as those with extensive tridimensional tissue loss need free muscle flaps because they conform better to such complex defects [5]. However, free fasciocutaneous flaps are reliable and effective for covering the less three-dimensional distal third and ankle open tibial fractures and can better tolerate the subsequent secondary surgical procedures [11,14,15,19]. It is also important to not underestimate donor-site morbidities [6,13,18]. Surgeon experience and familiarity with the flap should also be an important factor in flap selection. However, the dilemma of choosing between muscle and fasciocutaneous flaps is less relevant than identifying the patient that is at risk of a poor outcome and managing them appropriately [12–14,16]. Finally, there seem to be few significant differences between muscle and fasciocutaneous flaps or between local and free flaps [12,15,19–21]. Although not identified in the Search criteria the following article was felt to be important enough to be included, as it is a recent retrospective study of 39 patients with Gustillo IIIB tibial fractures, muscle flaps may be preferred over fasciocutaneous flaps in these patients. Radiographic assessment of these patients revealed a significantly greater percentage of patients treated with a muscle flap reaching fracture union by six months. There was no statistical difference between muscle and fasciocutaneous flaps at 3 or 12 months though [22]. However, local flaps are preferable in low velocity trauma and free tissue transfer appears to have advantages in high-velocity injuries [10,16].

Published studies on reconstruction of traumatic defects of the tibia are mostly retrospective studies with small, heterogeneous patient cohorts. A few of these compare muscle with fasciocutaneous flaps, but include a wide variety of patients and clinical indications, without sufficient details on the criteria used to select coverage of open tibial fractures [11,12,21]. The outcome measures between studies are different, as not all studies report time to union of the fracture, rates of deep infection or even flap survival. Overall, there is little difference in the clinical outcome with regard to infection rates, wound healing or fracture union, but no study is sufficiently powered to answer these questions. These parameters preclude meaningful systematic review or meta-analysis that can provide standardized guidance for the use of different flap options in the management of open fractures of the tibia [1,11].

To improve the patient's outcome, appropriate international consensus guidelines are required, breaking down also the length of hospital stay and the overall healthcare cost [1].

At this point, based on our understanding of the literature, we believe that different types of flap coverage after open tibial fractures have essentially equivalent and comparable outcomes in terms of flap survival, bone healing, stress fracture, infection, chronic osteomyelitis and donor site morbidity, with the timing of the coverage also being crucial. The type of flap should be based on the extent and the depth of the soft tissue defect, location of the fracture and surgeon experience.

More specifically, if we have to categorize them:

1. In low-energy trauma, local muscle or fasciocutaneous flaps should be considered the reconstruction of choice, if they are available.
2. In high-energy injuries such as open fractures of the tibia, muscle flaps may offer a more reliable reconstruction with fewer flap failures and lower reoperation rates. Free muscle flaps are more advantageous for the reconstruction of tridimensional bone and soft-tissue defects.
3. In patients with simple defects around the distal tibial or ankle, fasciocutaneous flaps may offer a better option.

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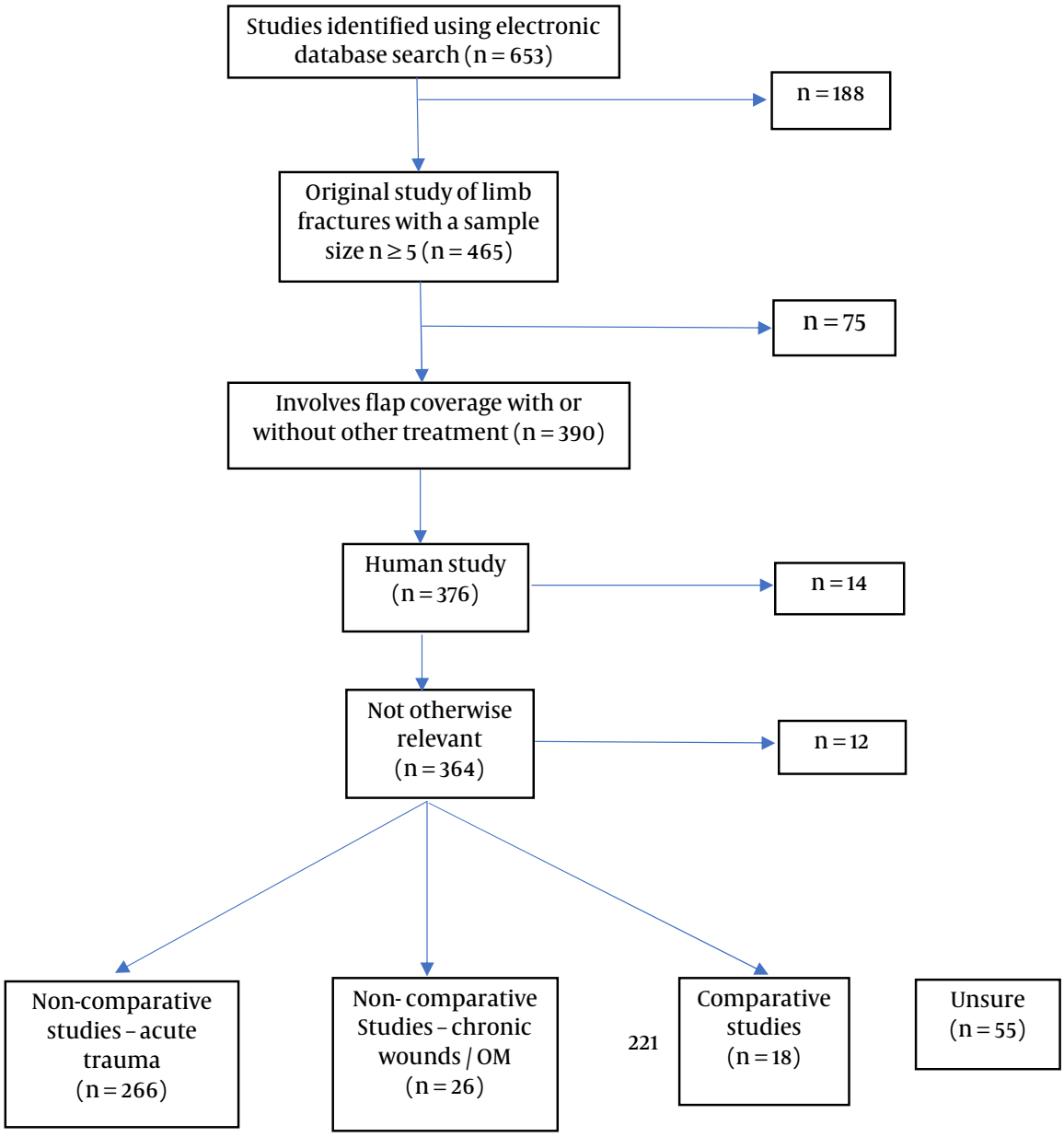

FIGURE 1. Flowchart of literature review.

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QUESTION 2: What is the appropriate timing for flap coverage of open fractures and traumatic wound defects?

RECOMMENDATION: The optimal time for wound coverage ultimately reflects when the wound has been appropriately cleaned and converted to a "living wound." Early flap coverage is preferred, ideally within 3-7 days, when patient and wound are suitable.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

The timing of soft tissue coverage has long been recognized as one of the most critical determinants of the length of in-hospital stay, most of the early postoperative complications and ultimate outcomes [1]. Early coverage has been associated with higher union rates, and lower complication and infection rates compared to those reconstructed after 5-7 days [2–5]. Furthermore, early reconstruction improves flap survival, as microsurgical free flap integration becomes more challenging with a delay due to an increased prothrombotic environment, tissue edema and the increasingly friable vessels. Only those patients presenting to facilities with an actual dedicated ortho-plastic trauma service are likely to receive definitive treatment of a severe open tibia fracture with tissue loss within the established parameters of good practice [6]. "Fix and flap" has sometimes been recommended for specialist hospitals where the expertise is available. Antibiotic bead pouches to decrease infection rates have long been advocated when there is segmental tissue loss, gross contamination or established infection as pre-flap tissue infection seems to be an independent predictor of adverse flap and skeletal reconstruction outcomes [7,8].

Level IV series of free tissue transfer to address open traumatic wounds with accompanying fractures have been published since the first free tissue transfer for soft tissue coverage by Buncke in 1970 [9]. In 1986, Godina advocated early soft tissue coverage on a review of 532 patients based on an increased rate of flap failure in those wounds open > 72 hours [10]. However, during that time period, infection management and particularly the care and treatment of osteomyelitis were poorly understood, and dogma existed that simply the placement of a free tissue transfer over infection in the form of infected hardware or osteomyelitis was enough to treat and cure the infection. It took a great deal of time to break this dogma. Various series advocate the need for early soft tissue coverage in these cases, due to exposed soft tissue as well as the results of higher flap failure and often accompanying late infection rate [11-13]. These studies are found to be flawed in multiple respects, which include the lack of expertise and knowledge in the diagnosis and treatment of existing infection [12], low volume with resultant lack of expertise [11,13] and the inaccurate conclusion that time of flap placement could in any way affect the probability of successful bony union.

Many good studies have appeared confirming what the experienced non-union surgeon and microsurgeon know: that flap survival depends upon a decolonized and "living wound." Harrison et al. performed a thorough literature review of articles published from 1995–2011, and performed meta-analysis of 15 articles meeting inclusion criteria. They reported no difference in outcome between when free tissue transfer was performed and survival of the flap or eventual outcome [14]. Theodorakopoulou et al. reported a systematic review of 11 studies of war-related high energy extremity injuries treated with free tissue transfer in the subacute period (9 days to 3 years post-injury). There was no direct association to time of flap placement with a 95.5% free flap success rate in this particularly complex patient population [15].

Since 2000, numerous independent case series by experienced microsurgeons have also shown no difference in outcome in regard to timing of free flap placement [16-20]. These represent well-executed tissue transfers except for one series with a higher overall but uniform flap failure rate [19]. The consistent finding was that timing of free tissue transfer was not a direct cause of failure of flap survival.

The original work of Godina seems now to be outdated and not applicable to current surgical practice as it relates to timing of free tissue transfer of traumatic wounds.

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Authors: Nathan O'Hara, David Lowenberg, Robert O'Toole

QUESTION 3: Should open fracture wounds be closed primarily or closed secondarily? If closed primarily, which ones and under what criteria?

RECOMMENDATION: Yes. Primary wound closure of many open fracture wounds appears to be a safe and likely beneficial strategy in the modern setting of improved debridement techniques, better methods of fracture stabilization, and improved utilization of early systemic antibiotic administration. It appears safe for lower grade open fractures and a subset of higher-grade open fractures when the wound is deemed appropriate for primary closure on a clinical basis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

METHODS

Randomized controlled trials, nonrandomized trials, prospective and retrospective observational studies were eligible for inclusion. We searched Medline, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to March 2018 for published studies without language restriction. Our search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) there was a comparison between patients with wounds closed primarily and secondary wound closure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in 303 papers. After removal of duplicates and screening of titles and abstracts, 12 articles were assessed and reviewed.

RATIONALE

The traditional practice of leaving all open fracture wounds open for repeat debridement at a later point in an effort to minimize risk of deep infection has changed over time. Many surgeons now routinely close most open fracture wounds at the time of initial debridement and fixation, particularly in lower grade open fractures and when wound severity and contamination are judged to be appropriate for primary closure.

A systematic review of the literature reveals no level I randomized trials in support of the practice of primary wound closure for open fractures, and the literature supporting this approach is consistently in favor of the practice, but it is also relatively weak. There is a group of more recent studies that has uniformly demonstrated lower surgical site infection rates with primary closure than with secondary closure for various open fractures in adults and children [1–7] and only one older study showing higher infection rates with primary closure [8]. However, all of these studies are methodologically limited as they do not account for selection bias between the less severe wounds that were closed primarily and the more severe wounds that were closed secondarily. As wound severity is very strongly associated with infection rates, this bias is important enough that results from these studies provide only limited insight on this issue except to point out that primary closure of some open fractures does not seem to be associated with high infection rates.

Other authors have provided similar data outlining low rates of infection utilizing a practice of primary wound closure in the vast majority of open fracture cases [9,10]. DeLong et al. used primary closure in 88% of type I, II and IIIA open fractures and had a 4% infection rate [9]. Similarly, Moola et al. used primary closure in 86% of 297 fractures and had a 4.7% deep infection rate [10]. However, while reassuring that primary closure of the majority of open fractures appears to result in an acceptable infection rate compared to historical controls, these studies are similarly methodologically limited as they lack a control group, so it is unknown if a practice of using more secondary wound closures in these patients would have resulted in a higher or lower infection rate.

One double-blind, randomized trial was published in 1993 using a factorial design to compare primary to delayed wound closure as well as the type of antibiotics used [11]. Although the random design is appealing, the sample size of only 82 patients with a low event rate presents a substantial risk of type II error and this study is very underpowered for the outcome of surgical site infection. The cohort only had two deep surgical site infections, so its conclusion that primary closure is safe is reassuring in that there was not a high infection rate in this group, but of limited value in comparing this practice to secondary closure.

The safety of primary closure was also demonstrated in a comparison between two South African trauma centers, one that used primary wound closure and one that did not [12]. This study also concluded that primary closure was safe, but again it was underpowered with a sample size of only 95 patients and an overall infection rate of only 3.3 % (3 patients). Therefore, there is significant risk of type II error with this study, and it therefore cannot provide

sufficient evidence regarding any potential difference in outcomes between the two closure strategies.

Two recent case-controlled studies provide the best evidence in support of this practice while attempting to address the issue of selection bias while also having adequate sample size and event rates to exhibit adequate statistical power. Jenkinson et al. used a propensity-matched cohort study design to demonstrate a lower infection rate in primary wound closure (4%) vs. secondary wound closure (18%, p = 0.0001) even after only including patients matched for likelihood of receiving delayed closure using propensity matching [13]. Scharfenberger et al. collected data prospectively and matched their patients to historical controls from a previous study on factors thought to predict likelihood of surgical site infection and also demonstrated that primary closure had a lower infection risk (4% vs. 9%, p = 0.001) [14]. Although both of these studies are methodologically superior to previous efforts to compare the effect of wound closure strategy on infection rates, the authors point out that there is still risk of unmeasured selection bias and a randomized trial is needed to rigorously compare the efficacy of these two closure strategies.

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APPENDIX – SEARCH STRATEGY (NO PUBLICATION DATE LIMIT)

Ovid Medline – 114 references retrieved on 03/14/2018
((open adj3 fracture*).ab,ti. OR "Fractures, Open".sh.) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) adj3 (closure*)).ab,ti **AND**
((infection* or sepsis).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Embase – 147 references retrieved on 03/14/2018
((open NEXT/3 fracture*):ab,ti OR 'open fracture'/de) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) NEXT/3 (closure*)):ab,ti **AND**
(infection*:ab,ti OR sepsis:ab,ti OR 'infection'/exp OR 'wound infection'/de OR 'cross infection'/de OR 'hospital infection'/de OR 'sepsis'/exp)

CINAHL – 29 references retrieved on 03/14/2018
((open W3 fracture*) OR MH Fractures, Open) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) W3 (closure*)) **AND**
(infection* OR sepsis)

CENTRAL – 13 references retrieved on 03/14/2018 – in Title, Abstract, Keywords
(open NEAR/3 fracture*) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) NEAR/3 (closure*)) **AND**
(infection* OR sepsis)

Authors: Daniel R. Schlatterer, Martin McNally, Gerard Chang, James K.K. Chan

QUESTION 4: What are the evidence-based recommendations for the use of negative pressure wound therapy (NPWT) in open fractures and traumatic wounds?

RECOMMENDATION: NPWT is an appropriate dressing in the short-term management (< 7 days) of complex traumatic wounds over open fractures, prior to definite soft tissue closure. NPWT is not superior to other sealed dressings and has increased initial cost.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)
Note: Please see Question 2 under Section 1.2. Prevention Risk Mitigation for additional rationale regarding NPWT.

METHODS

A comprehensive literature review was performed to identify all studies on the use of NPWT for the treatment of open fractures and traumatic wounds. We searched Ovid Medline, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2018 for published studies. The search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies

met the following criteria: (1) all patients included in the study had an open fracture or traumatic wound, (2) infection was an outcome variable and (3) NPWT was the intervention. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies without clinical follow-up/infection rates, and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in 247 papers. After removal of duplicates and screening of titles and abstracts, 26 articles were assessed and reviewed.

RATIONALE

Traumatic wounds and wounds over open fractures are at increased risk of developing infection due to contamination from injury, impaired blood flow, progressive soft tissue necrosis and prolonged exposure to hospital environment [1]. To minimize this risk, wounds are treated with thorough irrigation and debridement (I&D) followed by primary closure when possible or coverage with a graft or flap. Prior to definitive coverage, traditional occlusive dressings with sterile gauze had been the standard choice. Recently, there has been an increasing trend in using NPWT or vacuum-assisted closure (VAC) for wound management prior to coverage [2]. Proponents of this new method cite the following advantages to support its use: decrease tissue edema, enhance local blood flow, limit or prevent infection, improve flap rates and possibly reduce the overall need for flaps.

We performed a systematic review of the literature, as detailed above, to determine the evidence-based role of NPWT in the treatment of traumatic wounds and open fractures.

We found a group of studies supporting the use of NPWT in the treatment of traumatic wounds and open fractures. The study populations were a mix of children and adults with either traumatic wounds or open fractures, all of whom received NPWT. They found that NPWT was safe and effective and resulted in similar or lower infection rates, reduced flap complications, reduced graft size and decreased need for free flaps compared to historic controls [3–10]. However, while promising, all the studies were retrospective case series that were methodologically limited in that they lacked a comparative group and were retrospective in nature.

Eight studies compared NPWT to traditional gauze in the management of acute traumatic wounds or open fractures. Five were prospective randomized control trials, and three were retrospective case control studies. The three retrospective studies evaluated open tibia fractures and found NPWT to have significantly lower rates of infections (8.4-10 % vs. 22.6-33%), wound complications and flap failures compared to traditional gauze [11–13]. These findings are encouraging but are susceptible to the inherent limitations of retrospective studies, most notably selection bias.

The best evidence to support NPWT was found in four prospective randomized control trials comparing NPWT to traditional gauze in patients with acute traumatic wounds or open fractures. Three studies evaluated infection rate as an outcome. Two of the 3 studies showed significantly decreased infection rate with NPWT (4.6-5.4% vs. 22-28%) compared to gauze [14,15], while the other study found no difference between the two [16]. With regards to healing time, 2 of the prospective randomized control trials studied time to granulation as an outcome and both showed NPWT to be superior to gauze dressings [16,17].

With regards to duration of NPWT treatment, 3 studies retrospectively evaluated cases of traumatic wounds or open fractures treated with < 7 days of NPWT prior to wound coverage versus > 7 days of NPWT prior to wound coverage and compared them in terms of infection rate and reoperation rate. All 3 studies found a higher infection rate in cases treated with > 7 days of NPWT and concluded that while NPWT can be helpful in the management of traumatic wounds, its use should be limited to < 7 days or risk of infection increases [18–20]. However, all of these studies are methodologically limited, as they do not account for selection bias between the less severe wounds that were covered earlier and the more severe wounds that required longer time until coverage. As wound severity is very strongly associated with infection rates, this bias is important enough that results from these studies provide only limited insight on this issue. Another retrospective case series evaluated open fractures treated with I&D and NPWT prior to flap coverage. All patients had > 3 days, mean 18 days, of NPWT as they were treated on a delayed basis following stabilization and then transfer to their referral center for coverage. They found low rates of flap loss and infection, comparable to historical controls of patients treated with less than three days before definitive coverage [21].

There is an increasing body of data supporting NPWT as an adjunctive modality at all stages of treatment for traumatic wounds and open fractures. There is an association between decreased infection rates and decreased healing time with NPWT compared with gauze dressings. There is evidence to support NPWT beyond 72 hours without increased infection rates although prolonged use greater than 7 days may actually increase the risk of infection. At this time, NPWT use for traumatic wounds and open fractures requires extensive additional study.

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APPENDIX – SEARCH STRATEGY

Ovid Medline 221: (((open adj3 fracture*) or trauma*) adj3 wound*).ab,ti. or ("Fractures, Open".sh. or soft tissue injuries/) **AND** (NPWT or negative pressure wound therapy or VAC or (vac* adj3 clos*)).ab,ti. or negative-pressure wound therapy/**AND** ((infection* or sepsis).ab,ti. or Infection/ or wound healing/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Scopus 25: (open W/3 fracture* OR trauma* W/3 wound*) AND (npwt OR {negative pressure wound therapy} OR vac OR vac* W/3 clos*) AND (infection* OR sepsis OR wound* W/3 heal*)) in TITLE-ABS-KEY

CENTRAL 21: (open near/3 fracture* OR trauma* near/3 wound*) and (npwt OR "negative pressure wound therapy" OR vac OR vac* near/3 clos*) and (infection* OR sepsis OR wound* near/3 heal*) in in Title, Abstract, Keywords
Combined: 237

3.7. TREATMENT: OUTCOMES

Authors: Mustafa Citak, Carl Haasper, Kenneth Egol, William T. Obremskey, Hussein Abdelazia, Philip Linke

QUESTION 1: What is the most appropriate outcome measurement (clinical, radiographic, laboratory, etc.) for management of early infection after fracture fixation (IAFF)?

RECOMMENDATION: Fracture healing and infection control seem to be the most appropriate outcome measure to monitor the response to management of early IAFF. Secondarily, treatment success following infection management after fracture fixation is best assessed using a combination of the patient's clinical picture and laboratory examinations such as tissue cultures, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 70%, Disagree: 10%, Abstain: 20% (Super Majority, Weak Consensus)

RATIONALE

Regardless of the fracture site, primary fixation method, depth of the infection, culture results, nature of the fracture (closed or open) or chosen treatment algorithm for management of the infection, fracture healing seems to be the most appropriate final outcome measure for the treatment of an early IAFF. It must be noted that there remains substantial heterogeneity with wide variability in the definition of an early infection with regard to the time of its onset.

IAFF is one of the most serious complications in orthopaedic trauma surgery, which can impair fracture union, lead to poor functional outcomes or even result in loss of the extremity [1,2].

The management of IAFF and that of periprosthetic joint infection (PJI) differs from each other in some aspects. When treating an early IAFF, the primary aim should be the achievement of fracture healing to avoid delayed union or nonunion rather than immediate eradication of the infection [1,3].

Complicating infection management is the fact that there is no clear consensus with respect to what constitutes treatment success. Previous studies have defined the success of infection management based upon factors such as bony healing, clinical examination, culture results and the laboratory markers ESR and CRP.

To identify the best available outcome measure for the management of early infections after fracture fixation, we included all publications that reported on outcomes following management of early IAFF [4–37]. However, we found substantial heterogeneity in the definition of an early infection with regard to the time of its onset, one that varies from two weeks to five months [4,6,10,12,16,18,22,25–28,31].

Several papers reported on the clearance of the infection or its recurrence, either exclusively or with further outcome measures; other studies on the functional and clinical outcome or on the wound and soft tissue healing and few studies on the mortality rate. There are only limited number of reports on laboratory, microbiological or histological investigations as outcome measures [33,35–37].

It is important to note, that any cause of inflammation will trigger an increase in the patient's ESR and CRP. For example, surgery-related tissue damage and practices such as reamed intramedullary nailing have been shown to trigger a systemic inflammatory response and can lead to elevated ESR and CRP in the early postoperative period [36,37]. While the sensitivity of acute phase reactants for the presence of inflammation is high, non-infectious etiologies must always be considered. Recent studies have demonstrated that tissue

histology is one option for the confirmation of infection when tissue cultures are inconclusive; however, this technique is labor intensive and also prone to false negative findings [33,35].

The most common outcome measure in most studies was fracture healing or bony union [4–32]. The vast majority of identified studies have only a low to moderate level of evidence with retrospective case series designs and relatively small sample sizes. Moreover, measuring the outcome of a specific management strategy was the main focus of only a few studies. Regardless of fracture site, primary fixation method, depth of the infection, culture results, nature of the fracture (closed or open) or chosen treatment algorithm for the infection, outcome measures were extracted and analyzed. Due to the considerable heterogeneity, some descriptive analysis was also performed [4–32].

There were five studies with a relatively large case series. Rightmire et al., Berkes et al., Al-Mayahi et al., Hellebrekers et al. and, recently, Kuehl et al. reported on the outcomes after management of an early or acute IAFF of upper and lower extremity as well as pelvis and spine within the first four months in 69 patients, six weeks in 123 patients, five months in 71 patients, three months in 44 patients and three weeks in 49 patients, respectively. Besides the cure of the infection, fracture union was an important outcome measure in three of them. In the studies by Hellebrekers et al., Berkes et al. and Rightmire et al., in which open fractures were also included, fracture union was achieved in only 63%, 71% and 68% with implant retention, respectively. Implants had to be removed due to recurrence of infection in many cases [4,16,21,25,27].

The failure rate following IAFF of the ankle was 28% among the early infected cases (within the first six weeks), which could be related to persistence of the infection, a non-union or post-traumatic arthritis [22]. In the study by Zalavras et al., infection recurred in three of four identified infections within the first three weeks after ankle fracture fixation that had been managed with debridement and retention of the implant [9]. In contradistinction, Ziegler et al. have recently reported a 100% success rate with healing of ankle fractures without remissions following debridement and retention following IAFF that definitely occurred within three months after surgery [14].

Regarding IAFF with intramedullary nailing of the femur and tibia, there was only one infected non-union case from a total of 13 acute infections within the first month in the retrospective study performed by Chen et al. There was no significant difference regarding the time to fracture healing between cases with retention of the nail and those with nail exchange [31]. Among the included patients with infected intramedullary nails in the three older studies, only a few cases with an early infection within the first three weeks could be identified and delayed union had been observed [11–13].

In another prospective multicenter cohort study reporting on IAFF of the tibia, 56% of the fractures healed radiographically at one year, compared to 88% of those that were uninfected, and the time to union was significantly longer than that for the noninfected fractures. However, only 5 from 23 infected cases were reported to be early infections [15]. Delayed union was also observed in 3 out of 15 infected tibia and femur fractures treated with non-contact plates due to IAFF within 10 weeks after primary surgery [19].

Short- and long-term mortality rate was the outcome measure following management of IAFF within three months after surgery of the hip in the retrospective studies by Duckworth et al. and Edwards et al. [24,26]. Partanen et al. also performed a similar but matched control analysis although not all included cases were early infections. Beside the functional outcome and mortality rate, fracture healing was also analyzed. Failure to union was observed in 8 out of 19 cases, as infection most likely impaired fracture healing [29].

Deep early IAFF of proximal or distal humeral fractures treated by plate osteosynthesis had a high non-union rate, resulting in a poor functional outcome [20,28].

Pin tract infections in the form of K-wire fixation or external fixators can be managed conservatively and spontaneous fracture healing can be achieved with resolution of the infection [7,17,23].

Fracture union was also the common outcome measure to assess the success of management of IAFF of flat bones including the ribs, clavicle or mandible [5,18,30,32]. It can be evaluated both clinically and radiologically [5,10,14,16,17,25].

Even in late phases, the eradication of infection with restoration of an acceptable functional outcome is definitely the ultimate goal when treating an IAFF. Regardless, at this time fracture healing seems to be the most appropriate outcome measure in the case of an early infection. As soon as fracture healing is achieved, removal of the implant for the purpose of definitive eradication of infection can be considered.

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