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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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