THE ORTHOPAEDIC FORUM

Musculoskeletal Infection in Orthopaedic Trauma

Assessment of the 2018 International Consensus Meeting on Musculoskeletal Infection

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Abstract: Fracture-related infections (FRIs) are among the most common complications following fracture fixation, and they have a huge economic and functional impact on patients. Because consensus guidelines with respect to prevention, diagnosis, and treatment of this major complication are scarce, delegates from different countries gathered in Philadelphia in July 2018 as part of the Second International Consensus Meeting (ICM) on Musculoskeletal Infection. This paper summarizes the discussion and recommendations from that consensus meeting, using the Delphi technique, with a focus on FRIs. A standardized definition that was based on diagnostic criteria was endorsed, which will hopefully improve reporting and research on FRIs in the future. Furthermore, this paper provides a grade of evidence (strong, moderate, limited, or consensus) for strategies and practices that prevent and treat infection. The grade of evidence is based on the quality of evidence as utilized by the American Academy of Orthopaedic Surgeons. The guidelines presented herein focus not only on the appropriate use of antibiotics, but also on practices for the timing of fracture fixation, soft-tissue coverage, and bone defect and hardware management. We hope that this summary as well as the full document by the International Consensus Group are utilized by those who are charged with musculoskeletal care internationally to optimize their management strategies for the prevention and treatment of FRIs.

In 2013, the International Consensus Meeting (ICM) on Musculoskeletal Infection was held with experts from all over the world to formulate agreement on how to prevent, diagnose, and treat periprosthetic joint infection (PJI) and surgical site infection (SSI). That consensus meeting resulted in an article that was published in 2014[1]. A second ICM was held in Philadelphia in July 2018, which included other orthopaedic subspecialties such as trauma. The Delphi methodology (Table I) was utilized at both the first and second ICMs to determine the grade of recommendation (strong, moderate, limited, or consensus) and agreement among members on final recommendations[2] (Table II). The trauma group reviewed 49 questions and 30 systematic reviews to inform the consensus discussions. A document with recommendations was published in December 2018[3]. Below, we summarize the second ICM recommendations on the prevention, diagnosis, and treatment of fracture-related infections (FRIs), which are among the most common complications following fracture fixation and have a huge economic and functional impact on patients.

Prevention: Host Factors and Risk Mitigation

Open fractures are at high risk of infection. Preventative strategies and risk mitigation are critical. Modifiable patient factors

*A list of the VISION Investigators is included as a note at the end of the article.

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TABLE I Summary of the 2018 ICM's Adaptation of the Delphi Technique

Step	Time Frame	Description of Event
Selection of delegates	June 2016	Delegates from around the world were selected according to their publication track record in the field (≥5 publications in 5 years), specialty society nominations, and clinical expertise in taking care of patients with orthopaedic infections (defined by high patient volume). This initial step identified 953 delegates who were invited to participate in the process. Sixty-three delegates did not respond to the invitation and 21 declined to participate, leaving a potential consortium of 869 delegates from more than 90 different countries.
Identification of issues	December 2016 to April 2017	The delegates from all 9 subspecialties were asked to send 5-10 questions pertaining to topics on musculoskeletal infection. During this phase, a total of 3,210 questions were received.
Ranking of questions	April 2017 to August 2017	The collected questions were sent back to the delegates and ranked according to priority. In this process, duplicate questions were not removed and questions were not edited. Duplicate questions were regarded as representing higher question priority.
Evaluation of ranked questions	August 2017	After the ranking process, duplicate questions were removed. Question stems were rewritten according to the Delphi technique. This necessary step permitted the removal of suggestive words such as "What is the role of…?" as opposed to "Is there a role of…?" Upon the conclusion of this process, 652 questions comprised the final set of questions to be explored. Of this set, 16 questions were finalized for inclusion in the Pediatrics Section.
Assignment of questions	August 2017 to November 2017	The final set of questions were assigned to at least 2 delegates (per question) based on their publication track record and desire to research a specific question. The delegates were given specific instructions on how to conduct research on the topics presented in each question and how to write up the responses.
Systematic review	December 2017 to February 2018	Systematic review was executed by delegates using PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) methodology. During this time period, preliminary "responses" to questions were crafted. This process involved 14 delegates from the ICM.
Inter-delegate discussions	February 2018 to April 2018	Delegates assigned to each question shared their responses to each question and exchanged feedback. This "handoff" was coordinated centrally to create 1 document for both delegates to review. Through this process, over 6,000 emails were exchanged, underscoring the extent of communicating and coordinating that went into completing the document.
Document merging/ editing	April 2018 to June 2018	All received documents were merged and reviewed by an editorial board.
Document evaluation by all delegates	June 2018 to July 2018	Although the documents generated were posted on the website (www.ICMPhilly.com) for many months and available for view by EVERYONE (including the public), the final document was sent to the delegates and they were asked to review any and all questions that were posted live on the website. We received numerous comments from delegates during this period and implemented any and all appropriate changes to the document prior to the meeting.
Final premixing review/editing	July 2018	An internal editorial board reviewed the document in its entirety, and minor additional changes were made. The latest publications in the literature, up until June 30, 2018, were also checked and added to relevant sections.
Pre-vote discussion	July 25, 2018 to July 26, 2018	Delegates who traveled to the ICM met with their respective workgroups to discuss their section's questions over a 2-day time frame. During this time, questions were divided into 4 categories: (1) highly clinically relevant with little evidence supporting the recommendation, (2) highly controversial and clinically relevant, (3) highly relevant and with great supportive evidence for the recommendation, and (4) not clinically highly relevant with or without supportive evidence. During the meeting, only questions from categories 1 and 2 were discussed.
Voting	July 27, 2018	The process of voting was clearly explained by Dr. William Cats-Baril to the delegates prior to voting. All of the questions were presented to the present delegates prior to live in-person voting. The results of voting appeared on the screen shortly after the vote, with delegates electing to (1) agree, (2) disagree, or (3) abstain with the recommendation being presented.
Dissemination of consensus document	August 2018 to present	Following the meeting, the final document was updated to include voting results. In addition, outside editors from regarded journals in orthopaedics reviewed the document prior to its publication. The delegates were given the opportunity to review the final document over a 4-week period and to provide any additional feedback, and their suggestions were implemented into the document. The final document was then sent to various journals for publication and was printed in a consolidated textbook form. The final document has been translated to Spanish, Russian, and Ukrainian, with more languages to come in an effort to expand the accessibility and utility of the document.

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TABLE II Adapted Methodology from the American Academy of Orthopaedic Surgeons for Defining the Strength of the Recommendation and Evaluating It

Strength	Overall Strength of Evidence	Description of Evidence Quality*
Strong	Strong	Evidence from 2 or more "high" quality studies with consistent findings for recommending for or against the intervention.
Moderate	Moderate	Evidence from 2 or more "moderate" quality studies with consistent findings, or evidence from a single "high" quality study for recommending for or against the intervention.
Limited	Low-strength evidence or conflicting evidence	Evidence from 1 or more "low" quality studies with consistent findings or evidence from a single "moderate" quality study recommending for or against the intervention or diagnostic or the evidence is insufficient or conflicting and does not allow a recommendation for or against the intervention.
Consensus	No evidence	There is no supporting evidence. In the absence of reliable evidence, a recommendation is made on clinical opinion.

*Methods for assigning the quality of studies included in the definition for the strength of the recommendation are based on the type of study. Prognostic and diagnostic studies undergo the same quality appraisal, while observational and randomized studies are appraised the same way.

include tobacco product use and nutritional status. Minimizing tobacco and nicotine exposure and maximizing the nutritional status of the patient may decrease infection rates. Published evidence is conflicting, but tobacco and nicotine use may have a negative impact on health and potentially lead to an increased risk of infection. The Consensus Group agreed that smoking tobacco and any nicotine use increase the risk of infection following fracture fixation and, with the limited available data, that cessation of the use of tobacco and nicotine reduces complication rates[4-8].

Limited evidence supports that nutritional supplementation reduces the infection rate in well-nourished individuals, but there is moderate evidence that restoring nutritional balance in patients with poor nutrition might reduce the risk of infection. Proximal femoral fractures are common injuries in the elderly, and there is limited evidence that perioperative pneumonia, urinary tract infection, or ulcers increase SSI and/or PJI risk in patients who are treated with hemiarthroplasty or total hip arthroplasty. Limited evidence exists that a periprosthetic fracture increases the risk of joint or wound infection. The Consensus Group supported internal fixation rather than external fixation of periprosthetic fractures to decrease the risk of infection.

Moderate evidence indicates an increased risk of infection with the following factors: methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, the presence of an external fixator, the anatomical location of surgery (the pelvis or the axilla), and severe open fractures. In these situations, alterations in antibiotic prophylaxis can be considered.

MRSA colonization increases the risk of MRSA infection in elective cases. Current evidence that MRSA colonization increases the risk of acute infection in trauma patients is limited but suggests that decolonization may reduce FRI rates. Limited evidence supports bacterial decolonization in trauma patients to reduce FRI[9,10], particularly when surgery follows a period of temporary external fixation. Broadening antimicrobial coverage for elective procedures following the use of an external fixator may decrease the rate of MRSA infections.

Pelvic and groin procedures have a higher incidence of exposure to gram-negative bacteria, and moderate evidence supports the addition of gram-negative antibiotic coverage for these cases. *Cutibacterium* (formerly *Propionibacterium*) *acnes* is a common infection with surgical procedures that are performed near the axilla, and coverage for these organisms should be considered.

Open fractures have the greatest risk for FRI. Moderate evidence exists to support the use of local antibiotics and early wound closure for open fractures. Patients with multiple trauma may also have abdominal injuries. Limited evidence supports that performing internal fixation on fractures in a patient with an open abdomen does not increase the risk of FRI[11,12]. Gustilo-Anderson type-III open fractures have a higher infection rate, and limited evidence suggests recommending broad-spectrum antibiotics for prophylaxis in these injuries[13-15].

Diagnosis

Accurately estimating the impact of FRIs has been hampered by the lack of a clear definition[16,17]. The complexity and variety of FRIs may have hindered the establishment of uniform diagnostic criteria to develop such a definition, as was the case with PJI several years ago.

Currently, the lack of scientific evidence regarding the diagnosis of FRIs has precluded the development of evidence-based diagnostic criteria. A small number of studies evaluating serum inflammatory markers, tissue and sonication fluid sampling, and imaging modalities are available[18-21]. To our knowledge, validation studies on clinical parameters do not exist. Therefore, an expert group composed of scientific and medical organizations (the FRI International Consensus Group) was convened to develop a consensus definition. This resulted in a definition that was based on confirmatory (infection definitely present) and suggestive (infection possibly present) criteria[22]. Recently, the definition was updated to include histological confirmation of >5 polymorphonuclear neutrophils (PMNs) per high-power (×400) field as a confirmatory sign in chronic/late-onset cases

(i.e., fracture nonunion) and nuclear imaging signs as suggestive of FRI[23-25] (Fig. 1, Table III).

Developing separate diagnostic criteria that are based on time for acute/early infections and chronic/late infections (i.e., infected nonunion) is arbitrary, so a single definition for FRI was preferred. Time from surgery/injury is one factor that a clinician incorporates into treatment decisions. A distinct time frame that differentiates acute and chronic infection is not available in the current literature.

A strong consensus supported that the diagnostic criteria proposed by the International Consensus Group on FRI should be used to determine the diagnosis of infection after fracture fixation[20,22,25]. With fracture nonunion, moderate evidence supports the use of the same FRI diagnostic criteria. The combination

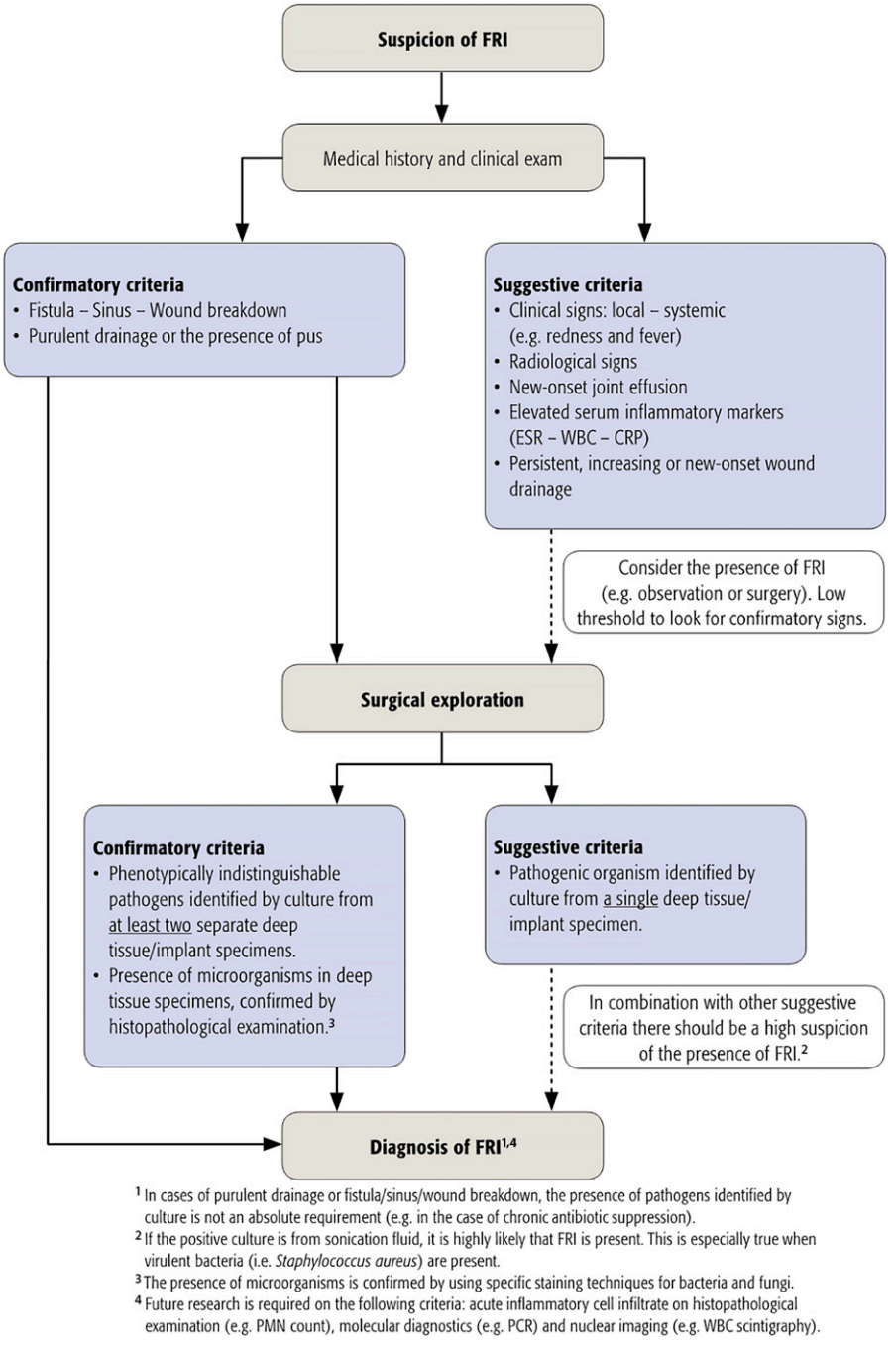

Fig. 1

Diagnosis of fracture-related infection (FRI)[22]. ESR = erythrocyte sedimentation rate, WBC = white blood cells, CRP = C-reactive protein, PMN = polymorphonuclear leukocytes, and PCR = polymerase chain reaction.

TABLE III Diagnostic Criteria for Fracture-Related Infection*[25]

Confirmatory Criteria	Suggestive Criteria
Clinical signs: - Fistula - Sinus - Wound breakdown - Purulent drainage or the presence of pus Microbiology: - Phenotypically indistinguishable pathogens identified by culture from at least 2 separate deep tissue/implant specimens Histopathology: - Presence of microorganisms in deep tissue specimens, confirmed by using specific staining techniques for bacteria and fungi - Presence of >5 PMNs/HPF in chronic/late-onset cases (e.g., fracture nonunion)	Clinical signs: - Local/systemic (e.g., local redness, swelling, fever) - New-onset joint effusion - Persistent, increasing, or new-onset wound drainage Laboratory signs: - Increased serum inflammatory markers (ESR, WBC, CRP) Radiographic and/or nuclear imaging signs Microbiology: - Pathogenic microorganism identified from a single deep tissue/implant specimen

*ESR = erythrocyte sedimentation rate, WBC = white blood-cell count, CRP = C-reactive protein, PMNs = polymorphonuclear neutrophils, HPF = high-power field.

of the consensus definition of FRI with the definition of nonunion should be used; however, the definition of nonunion varies, and both the FRI consensus definition and any criteria of an infected nonunion will need scientific validation.

Historically, the Gustilo-Anderson classification of severity of injury in open fractures has been utilized as a predictor of infection and amputation[26,27]. The Orthopaedic Trauma Association (OTA) Open Fracture Classification (OFC) was introduced in 2010 as a mechanism for describing all open fractures[28]. Instead of a single composite score, the OTA-OFC consists of 5 separate components (i.e., skin, muscle, arterial, contamination, and bone loss).

Limited evidence indicates that the OTA-OFC is more consistent than the Gustilo-Anderson classification. Current data suggest that the OTA-OFC provides a more complete description of the injury with interobserver agreement that is better than the Gustilo-Anderson classification for predicting early amputation and the need for additional surgery.

Treatment

Antibiotics and Nonoperative Management

The use of antibiotics for reducing infection rates has strong support from numerous studies. Timing and antibiotic choice, however, are 2 areas of debate. Patients with Gustilo-Anderson type-III open tibial fractures who are given systemic antibiotics at >66 minutes after presentation with an open fracture are at substantial risk of FRI. Moderate support exists for administering antibiotics as soon as possible. There is strong support for recommending administration of a first-generation cephalosporin for Gustilo-Anderson type-I to III fractures[29]. There is limited evidence for the additional use of systemic gram-negative coverage in Gustilo-Anderson type-III fractures to prevent infection. Systemic aminoglycosides may risk nephrotoxicity, especially in the presence of hypotension, hypovolemia, and renal dysfunction[14,30].

The current literature moderately supports stopping prophylactic antibiotics after 24 hours in patients with type-I and type-II fractures and after 72 hours in patients with type-III injuries. Continuing antibiotic use for 24 hours after wound closure is supported, but not beyond this time frame, regardless of open fracture type.

Moderate evidence supports the use of local antibiotics in patients with open (contaminated) or infected fractures. A recent meta-analysis demonstrated a fourfold reduction in infection rates in all 3 types of open fractures, mainly with use of polymethylmethacrylate (PMMA) with gentamicin[31].

Antibiotic selection should be pathogen-specific. No evidence suggests that a 3-month duration of therapy is more effective than 6 weeks. In addition, limited evidence indicates that oral medication is equivalent to intravenous therapy[32]. Additionally, minimal evidence supports the efficacy of hyperbaric oxygen in the treatment of FRI since only 1 case series has been published since 2004[33].

Surgeon and Care Team

Many FRIs occur in patients with complex medical and psychosocial needs, requiring input from multiple specialties (orthopaedic trauma, plastic surgery, infectious diseases, vascular, pharmacology, and specialist nursing). In some complex cases (infected nonunions, pelvic infections, or infected segmental bone loss), the reconstructive options are technically demanding and may be better concentrated in a limited number of centers. Limited evidence supports that care for patients with an infected nonunion in specialized centers improves outcomes[34-36].

The International Consensus Group supports a multidisciplinary team of expert providers of care for patients with infected fractures and nonunions, including surgeons who perform bone reconstruction and soft-tissue reconstruction,

infectious disease specialists, and musculoskeletal radiologists. The exact members of the group and other specialists who are required will depend on a patient's needs and local history, resources, and preferences[34,37].

Risk Factors

Limited evidence exists that revision joint arthroplasty, preoperative anemia, increased age, a high comorbidity index, a low body-mass index, female sex, and long surgical time are predictors of allogeneic blood transfusion in patients with periprosthetic fractures[38,39]. Minimally invasive surgery decreases the risk of blood transfusion[40-42].

Limited evidence also indicates that infection rates are higher in patients receiving arthroplasty for acute femoral neck fractures compared with hip arthroplasty for arthritis[43]. The reported infection rate is significantly higher in patients with periprosthetic fractures.

Procedure-Related Care

The Consensus Group investigated the effect of open fracture care, the management of established FRI, the timing of change from external fixation to internal fixation, surgical options to avoid segmental resection during debridement of osteomyelitis, preferred methods for the reconstruction of posttraumatic segmental bone defects, and the best time interval between procedures during the staged management of chronically infected fractures.

The literature strongly suggests that urgent debridement is needed in the initial treatment of open fractures, but the optimal time from injury to debridement remains unknown. Little evidence supports an arbitrary 6-hour deadline. Paradoxically, moderate evidence supports that delayed debridement beyond 8 hours could increase infectious complications, especially with type-III open tibial fractures. In the emergency room, open fractures should be irrigated to remove all gross contamination prior to applying dressings and splints. In patients with Gustilo-Anderson type-I, II, and IIIA/B open fractures, irrigation with normal saline solution (using gravity flow irrigation) should be performed[44,45]. Six liters is a reasonable volume to use, but larger wounds and gross contamination may require proportionately more. Bactericidal irrigation (chlorhexidine, povidone-iodine, and antibiotics) has not been adequately studied in patients with open fractures, but basic and clinical studies raise concerns that these additives may damage tissue and increase reoperation rates[46,47].

The timing of conversion from temporary external fixation to definitive fixation should be based on the patient's condition (concurrent injuries, premorbid health and function), the injury characteristics (location, soft tissue, wounds) as well as appearance, and the placement of pin sites.

The interval between the first and second stages in the treatment of infected nonunions with a bone defect with use of the intramedullary (IM) technique should be dependent on infection status and the condition of the local soft tissues. The optimal time is not known, but current recommendations are for the second stage to be performed between 6 and 12 weeks after the initial stage. To our knowledge, no studies have assessed the optimal timing of bone-grafting in the management of infected nonunion. No data support a time frame earlier than 4 weeks; some case series recommend an interval of 7 to 8 weeks. Most studies range between 6 and 12 weeks following the initial debridement[48-51]. Scientific data based on an animal model indicate that growth factors peak at 4 weeks using the IM technique[52].

Management of Hardware

Whether to remove or retain hardware that is associated with FRI is a common dilemma that orthopaedic surgeons must address. Basic science data indicate that biofilm will prevent the eradication of infection if the hardware is retained[53]. Although the evidence is limited, several retrospective clinical studies indicate that in selected cases, hardware can be retained after operative debridement and the infection can be suppressed until bone healing. The optimal treatment strategy for trauma patients with early FRI is to perform a thorough debridement, tissue culture sampling, and empiric antibiotic therapy, and to retain hardware if the construct is stable[54,55]. When the fixation is unstable, treatment should include surgical debridement with removal of loose implants, stabilization with revised internal or external fixation (immediate, staged, or delayed), antibiotic therapy, and soft-tissue coverage, if necessary. It is not appropriate to retain unstable implants, even if the infection presents within a few days of primary fixation.

The consensus agreement was that the removal of implanted hardware in patients with FRI should be considered if the hardware is obviously loose or the bone is unlikely to heal with the current fixation. Strong consensus supports that the decision to retain or remove hardware differs by clinical scenario and is based upon the extent of the infection, instability of the hardware, and fracture site[3]. Moderate evidence indicates that after debridement, the addition of rifampin in patients with staphylococcal infections is beneficial if an implant is present[56]. If the fracture has healed, all hardware and necrotic material can be removed, with high rates of resolution of infection.

Open tibial shaft fractures have some of the highest rates of infection. There is strong evidence that no difference in infection rate exists with the use of reamed or unreamed tibial nails in open fractures[57]. In addition, no difference in infection rate is seen in patients with Gustilo-Anderson type-I or II open fractures that are treated with either circular external fixation or unreamed or reamed IM nails. There is limited evidence that Gustilo-Anderson type-IIIA/B fractures have a lower infection rate with circular external fixation compared with the use of plates and screws or IM nails[58,59].

Limited evidence supports the use of antibiotic-coated rods (ACRs) or antibiotic-coated plates (ACPs) for stabilization, either after single-stage debridement and revision fixation or with reimplantation after infection eradication. The ideal mixture and concentration of antibiotics in bone cement are not known. There was consensus agreement that,

when utilizing an antibiotic spacer or antibiotic-coated implant, 2 g of vancomycin and 2.4 g of an aminoglycoside should be added to each pack (40 to 70 g) of PMMA cement. One should plan to remove a temporary ACR and replace it with a more stable construct once the infection has been controlled[60]. If the ACR (locked or unlocked) is stable and the nonunion heals, it may be left in place or removed on an elective basis. Recently, implants coated with absorbable antibacterial coatings have been studied, but additional evidence is required before a recommendation can be made.

Soft-Tissue Wound Coverage

Primary wound closure is moderately recommended if there is adequate soft tissue. It can be performed safely at the time of definitive fixation of noncontaminated fractures[61,62]. If primary closure is not possible, it is preferable to use a local pedicled flap for reconstruction, such as a gastrocnemius flap in the upper portion of the tibia[63]. However, these flaps often are compromised by the injury, subsequent treatment, or infection.

There are few well-designed trials that allow for a valid comparison among any types of free flap. The published studies do not give a clear indication as to how the flap type was selected, but they do suggest that different wounds require different types of flaps.

Overall, moderate evidence indicates that little difference exists in the clinical outcome in terms of infection rates, wound-healing, or fracture union rate among flap types; to our knowledge, no study has been sufficiently powered to provide these answers.

Fasciocutaneous flaps have a higher rate of wound complications (44% compared with 23% after muscle flaps), require more reoperations (4 times more), and often leave a poor cosmetic result at the donor site[64-66].

In animal models, muscle flaps have been shown to increase bone formation (50% more) around fractures and are better at eradicating bacteria from contaminated open fractures when compared with fasciocutaneous flaps[67].

Moderate evidence indicates that soft-tissue coverage is ideal within 3 to 7 days of injury with a Gustilo-Anderson type-IIIB open tibial fracture when the wound is "clean" and the patient is stable[66,67]. In type-III open fractures of the tibia, muscle flaps have strong support because they may have fewer flap failures and lower reoperation rates. In patients with simple defects around the ankle, moderate evidence supports that fasciocutaneous flaps may have lower failure rates[64-66].

Additionally, moderate evidence indicates that the use of negative-pressure wound therapy (NPWT) should be limited to no longer than 7 days after open fracture[68-73]. Standard sealed surgical dressings without negative pressure are an acceptable alternative[69,71].

Overview

This paper is a summary of the Consensus Group's full document. Clinicians can use this summary as well as the full document to help make evidence-based decisions on patient care for infection prevention and treatment. The recommendations are not all "strong" because the literature is not complete on this important topic. Additional work needs to be performed; this summary and the full document help to identify the areas that need further investigation. ■

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Update

This article was updated on July 2, 2020, because of previous errors. On page e44(4), in the legend for Figure 1, the sentence that had read "Diagnosis of fracture-related infection (FRI)." now reads "Diagnosis of fracture-related infection (FRI)[22]." On page e44(5), the title for Table III that had read "Diagnostic Criteria for Fracture-Related Infection*[14]" now reads "Diagnostic Criteria for Fracture-Related Infection*[25]."

An erratum has been published: J Bone Joint Surg Am. 2020 Aug 5;102(15):e93.