

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) (PDLA)/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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