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Mini-Review

Pre-hospital systemic antibiotic prophylaxis for penetrating trauma: Is the military usage applicable to civil emergency medical services? A mini-review

Jonah Klaus, Stefan Bereswill and Markus M. Heimesaat*

Institute of Microbiology, Infectious Diseases and Immunology, Gastrointestinal Microbiology Research Group, Charité - University Medicine Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.

ABSTRACT

In the military, pre-hospital systemic antibiotic prophylaxis (SAP) is used in penetrating injuries or open fractures to prevent infections but is not practiced in civil emergency medical service (EMS). We therefore performed a literature survey of the Pubmed database and assessed studies evaluating the correlation of early, on-scene antibiotics and the infection rates in patients suffering from penetrating injuries or open fractures. Our survey revealed that i.) in case of open fractures there is evidence for pre-hospital SAP reducing the infection rates which not also holds true for the military, but also for the civil EMS; ii.) a time frame from incident to SAP of less than 60 minutes was most important for the effectiveness of SAP; iii.) it is likely that the benefits of prehospital SAP for open fractures might apply to many types of penetrating injuries; iv.) the usage of pre-hospital antibiotics in the civil setting is considered as safe and relatively cheap and can easily be provided by professional health care takers. In conclusion, the pre-hospital antibiotic prophylaxis in open fractures and penetrating injuries might be easily implemented in the civil EMS settings. Future studies with bigger cohorts, however, are needed to further support these findings.

*Corresponding author: markus.heimesaat@charite.de

KEYWORDS: pre-hospital systemic antibiotic prophylaxis, civil emergency medical services, penetrating traumatic wounds, open fractures, infection rates.

INTRODUCTION

Penetrating injuries are still at high risk for infection. For example, the numbers of infection after penetrating abdominal trauma vary from 4% to 31% [1]. For combat-related type III open tibia fractures, the deep wound infection rate was found to be 27% [2], whereas for type III open fractures in general [3], the infection rate was shown to vary from 9% to 50% [4]. A study from 1998 revealed an annual incidence of 11.5 infections per 100,000 open fractures [5], whereas a systematic review from 2017 demonstrated an incidence for penetrating injuries of 330/100,000/year [6].

It is well known that antibiotic prophylaxis improves the infection-related outcome after open fractures and surgical interventions [7] and that the risk for infection increased dramatically 5 hours after colonization of the wound [8]. In addition to the 5-hour timeframe some studies revealed an antibiotic administration within 3 hours as the most important prerequisite in order to prevent from infection [9, 10]. Due to the extensive study situation antibiotic prophylaxis for open fractures is also suggested in the level 3 guideline on the treatment of patients with severe and/or multiple injuries [11]. Very little, however, is known about the actual advantages of reducing the time from injury to the first antibiotic application below the aforementioned 3 to 5 hours. Furthermore, the effects of pre-hospital antibiotic application for penetrating injuries are scarce.

In the military combat situation, there is a wide range of possible injury mechanism, but most injuries are associated with penetrating traumata. For example, 73% of the injured soldiers from the Israeli Defense Forces serving in the second Lebanon war suffered from penetrating injuries [12]. The high percentage of penetrating injuries associated with the high infection rates mentioned above makes an adequate antibiotic prevention strategy necessary. Therefore, antibiotic prophylaxis is recommended as soon as possible for open combat wounds in clinical practice guidelines all over the world [13, 14]. However, the actual implementation is usually not as extensive as the guidelines recommend, as can be seen in the Israeli Defense Force given that only a fraction of those patients with immediate antibiotic indications also receive antibiotics [15]. This is not only a problem for infection prevention but also regarding the availability of data in terms of the effectiveness of prehospital antibiotic application. Although no antibiotics have been applied in many cases, on-scene administration of antimicrobial compounds has long been practiced in the military and is still practiced today. There are two major problems facing each other in terms of fighting infections, namely the risk of major infection on the one hand and the risk of antibiotic resistance upon antimicrobial treatment on the other. If early antibiotics reduced the rate of infections, it could also reduce the numbers of cases needing extended antibiotic treatment and therefore the risk for subsequent antibiotic resistance, thus implicating an important strategy in times of progressively rising antibiotic resistances.

In the civil emergency medical services (EMS) antibiotic prophylaxis is not common. But the usage of pre-hospital antibiotics in the civil setting is considered as safe and relatively cheap [16] and can easily be provided by professional health care takers. Hence, the prehospital application of antibiotics might be easily implemented in most civil EMS settings.

The aim of the present survey was therefore to assess whether the pre-hospital application of antibiotics for penetrating traumata including open fractures, as it is practiced in the military, could also be transferred to the civil EMS service.

METHODS

Inclusion and exclusion criteria

Inclusion criteria for this mini-review were studies evaluating penetrating trauma or open fractures combined with on-scene administration of antibiotics. Studies evaluating the prophylactic administration of antibiotics in the hospital were excluded given that in many cases the time from incident to antibiotics had not been evaluated.

Search strategy

A systematical online literature search was conducted from November 27 to December 5, 2019 applying the PubMed database. The aim was to assess studies evaluating the correlation of early, on-scene antibiotics and the outcome of patients suffering from penetrating injuries or open fractures. The search included studies from 2009 until 2019. Firstly "(preclinical OR prehospital OR (on scene)) antibiotic" was searched. Then, synonyms were also included with the Boolean operator OR and the MeSH term. Subsequently, the search was extended to include the term "(penetrating (trauma OR injury))" in order to be able to limit the search results to specific injury patterns. The Boolean operator AND ensures that both terms must be included in the results. In addition to the injury patterns, the term "OR (open fracture)" was added, as it is often listed to separate penetrating injuries. Exclusion criteria were the prophylactic, but not prehospital application of antibiotics and the unavailability of free full text. In consequence 15 items were found. After evaluating all 15 articles regarding the inclusion criteria and the exclusion criteria three articles were included (Figure 1).

Data extraction

The data were extracted using a spreadsheet program including study design, setting and inclusion/ exclusion criteria of the studies. To evaluate the findings, time until start of antibiotic application, infection rates, patient's age and other epidemiologic

Search	Actions	Details	Query	Results	Time
#4	•••	›	Search: **(preclinical OR prehospital OR (on scene)) antibiotic AND ((penetrating (trauma OR injury)) OR (open fracture))** Filters: **from 2009 - 2019**	15	02:59:46
#3	•••	›	Search: **(preclinical OR prehospital OR (on scene)) antibiotic AND ((penetrating (trauma OR injury)) OR (open fracture))**	26	02:59:40
#2	•••	›	Search: **(preclinical OR prehospital OR (on scene)) antibiotic AND (penetrating (trauma OR injury))**	11	02:58:32
#1	•••	›	Search: **(preclinical OR prehospital OR (on scene)) antibiotic**	3,326	02:57:45

Figure 1. Boolean logic search results on PubMed data base.

factors, if available, were extracted as well as the main conclusion(s). The extracted data sets are presented in the results section as follows.

RESULTS

Gerhardt *et al.*

The retrospective cohort study by Gerhardt and coworkers [17] was the only one out of the 3 studies within a military setting, including patients undergoing medical treatment for penetrating combat wounds who were able to return to duty after initial treatment. Insulated burn or eye trauma was excluded. The setting of the study was an urban combat in central Iraq from March 31, 2004 to February 15, 2005. Altogether, 53 patients were included with patient ages within an interquartile range from 19 to 25 years. The patient outcomes defined as <48 hours until development of infection were evaluated depending on early SAP and wound irrigation.

As shown in Figure 2 a clear reduction of the infection rates was assessed when SAP was applied. For patients without administration of SAP the infection rate was as high as 40%, whereas, remarkably, only 7% of patients developed an infection upon SAP (confidence interval of 95%). The classes of the antibiotics the soldiers had been treated with varied; in most cases a third-generation cephalosporin such as ceftriaxone or fluoroquinolones were administered. One needs to take into consideration, however, that the numbers of individuals in the respective cohorts were rather small and no specific data for the exact time point of antibiotic application were available. Nevertheless, when following the clinical practice guidelines, SAP is likely to be administered well below an hour post incident. Hence, less patients developed an infection after administration of SAP in soldiers suffering from penetrating combat wounds. Furthermore, there are combined and independent associations between wound irrigation, SAP and decreased infection rates.

Thomas *et al.*

Thomas *et al*. [18] performed a prospective, nonrandomized, nonintervention multi-center cohort study of patients with suspected open extremity fractures, evaluating the clinical outcome depending on the time point of initiation of antibiotic treatment. The study assessed the outcome of antibiotic treatment initiated already by civil helicopter emergency medical service (HEMS) as compared to arrival in the hospital and was performed in the USA and Canada from July 2009 to June 2010. Altogether, 138 patients were included with a median age of 46 years. Due to incomplete follow-up only 83 patients could be included in the final evaluation. As clinical endpoints, an acquired infection or non-union of fracture within 6 months of follow-up were defined. The third-generation cephalosporin ceftriaxone was the only antibiotic given.

The absolute risk reduction of infection was 5.2% when antibiotic treatment was initiated by the HEMS crew (7.7% infection rate) when compared to the hospital setting (12.9% infection rate) as shown in Figure 3 (difference not significant). The time from incident to first antibiotic application was

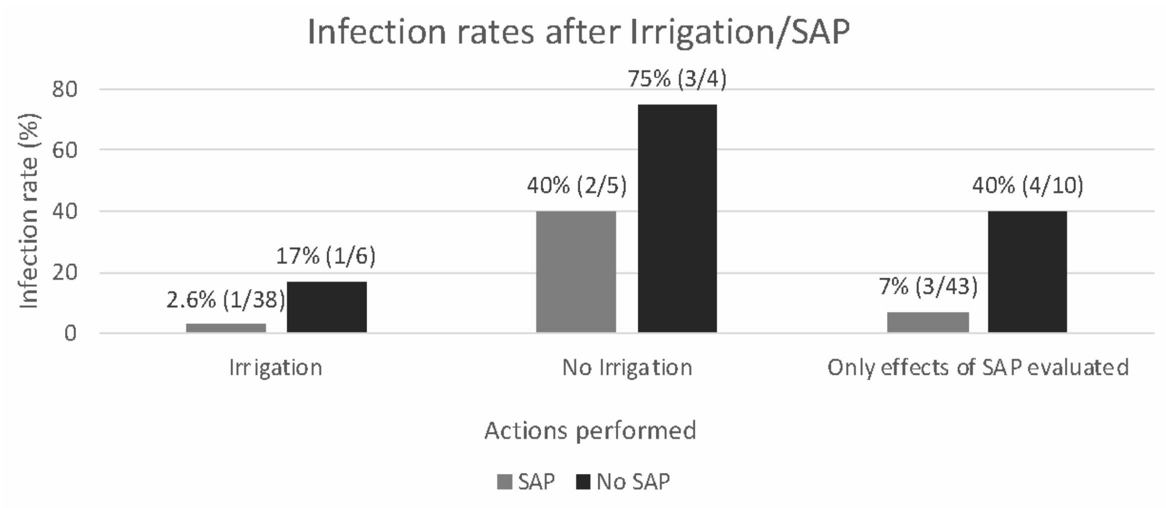

Figure 2. Study by Gerhardt *et al.* [17], surveying the infection rates within 48 hours after incident for soldiers suffering from penetrating trauma in the combat situation after irrigation and systemic antibiotic prophylaxis (SAP). The findings are statistically significant if exclusive effects of SAP were evaluated. Upon SAP 3 out of 43 patients (7%) developed an infection, whereas without SAP 4 of 10 (40%) acquired an infection.

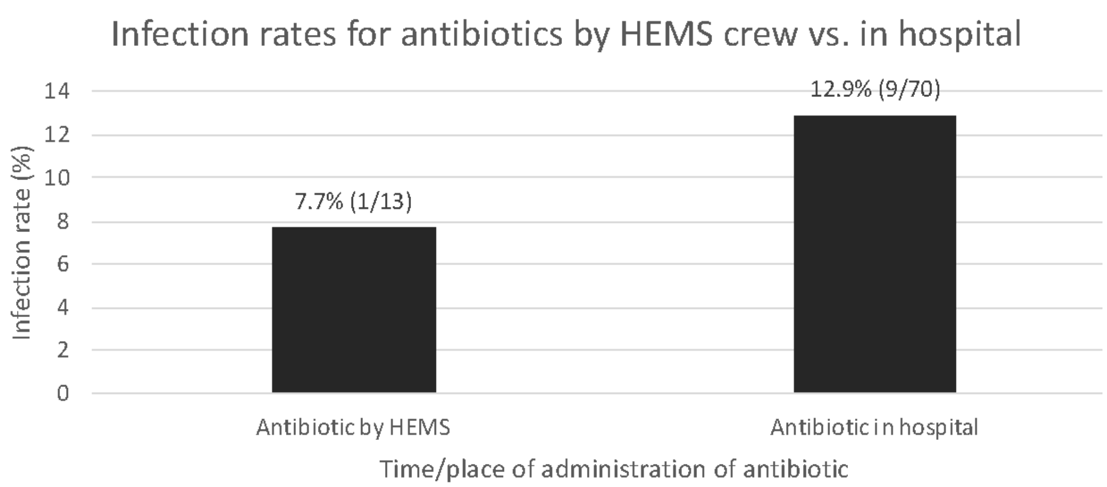

Figure 3. Study by Thomas *et al.* [17] comparing infection rates for patients with open fractures treated with antibiotic by helicopter emergency medical service (HEMS) crew versus hospital setting. One out of 13 patients (7.7%) treated with antibiotics by the HEMS crew developed an infection as compared to 9 out of 70 patients (12.9%) having received antibiotic treatment in the hospital (difference not statistically significant).

also evaluated. If antibiotics were administered by the HEMS crew the average time from incident to antibiotic was 47 minutes with an interquartile range from 37 to 60 min. In case antibiotic treatment was initiated at the hospital, the first dose of antibiotic was considered to be given within 5 minutes upon arrival in the emergency department. The evaluated average time of in-hospital start of antibiotic application, however, was 77 minutes with an interquartile range from 65 to 92 minutes. Although the assessed differences were not statistically significant, the study could still reveal a trend towards the effectiveness of prehospital antibiotic treatment of patients with suspected open extremity fractures in the civil EMS and should be reproduced with a larger cohort to potentially prove the findings.

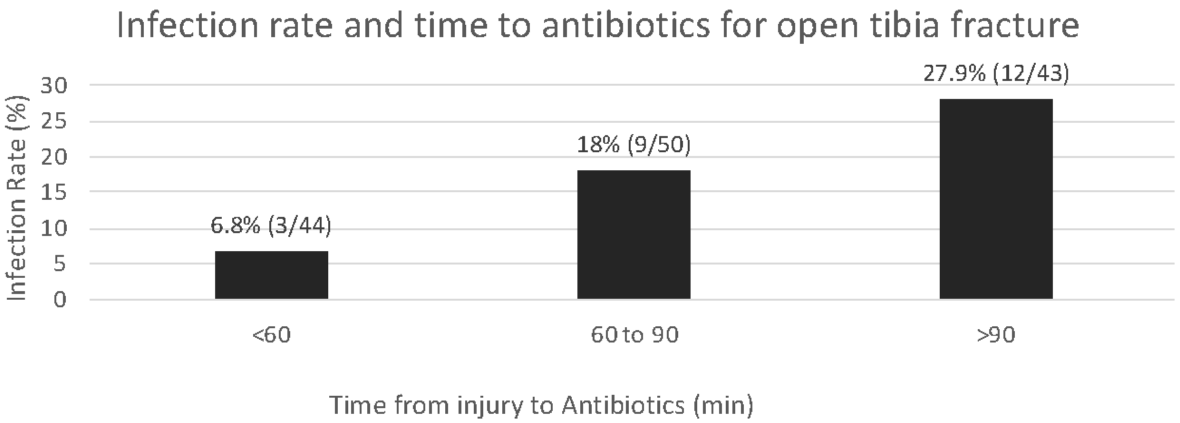

Figure 4. Study by Lack *et al*. [4] assessing the correlation between the time of initiation of antibiotic treatment in patients with type III open tibia fractures and infection rate. For patients receiving antibiotics within 60 minutes following fracture 3 of 44 (6.8%) developed an infection, whereas this was the case in 12 out of 43 (27.9%) of patients receiving antibiotics later than 90 minutes after the incident. The findings are statistically significant if the early (< 60 min) and the late group (> 90 min) are compared.

Lack *et al*.

The retrospective prognostic study by Lack *et al*. [4] investigated the importance of the timeframe in which an antibiotic compound was administered in case of type III open tibia fractures. The study included type III open tibia fractures treated at a level 1 trauma center in the USA between January 2013 and December 2013. A 90-day follow-up monitoring of surgical site deep infection was performed. The median age of patients receiving antibiotics within an hour was 34 years and for patients receiving antibiotics the median age was 42 years. Epidemiological factors (age, smoking, diabetes, injury severity score, type IIIA versus IIIB/C injury, and time to surgical debridement) were not associated with infection rates. The antibiotic delay of 66 minutes was considered most predictive for acquisition of an infection. The obtained results were significantly different when comparing the outcome in the early (< 60 min) and the late group (> 90 min) as shown in Figure 4.

There was a total risk reduction of infection by 21.1%. In 130 out of 137 patients, antibiotics were administered within 3 hours after injury. The time from injury to arrival in the trauma center was also evaluated: 42.3% (58/137) of the patients arrived at the trauma center within 60 minutes. In most cases (93.4%), the first-generation cephalosporin cefazolin was the administered antibiotic agent. Hence, a significant reduction of infection rates in patients suffering from type III open tibia fractures could be assessed if SAP was administered within an hour instead of 90 minutes or later after incident.

DISCUSSION

Main findings

Of the three studies included, two were performed in the civil and one in the military emergency setting. The studies evaluated the benefits of prehospital SAP of combat-associated penetrating injuries, of open fractures in general and of type III open tibia fractures in particular. Two studies showed statistically significant results with regard to the benefits of early prehospital SAP. One study, however, did not reveal statistically significant findings, but still showed a trend towards the positive effects of prehospital SAP. In most cases first or third generation cephalosporines were applied. A time frame from incident to SAP of approximately less than 60 minutes was most important for the effectiveness of SAP. If the time from incidence to hospital was assessed, however, most patients were shown not to arrive in the hospital within an hour.

Other reviews

The review by Smit and Boyle [19] was published in 2014 and included data from January 2000 to March 2013 addressing whether prehospital SAP was associated with a better outcome for patients with penetrating and/or open wounds and included four studies within the combat setting and if these results can be transferred to a civil setting. The authors found sparse evidence proving the effectiveness of antibiotic prophylaxis for open wounds in the civilian pre-hospital setting and concluded that further research needs to be undertaken to support their findings.

Military setting

In the military setting a lot of personal patient data are known, such as medical history including existing allergies and blood group. This makes it easier to provide a fast, effective and safe treatment for major injuries. In terms of prehospital antibiotic prophylaxis, this means that potential allergies against antibiotic compounds are known and therefore, the appropriate and safe antibiotic agent can be chosen based upon this knowledge. In many cases soldiers carry an individual first aid kit (IFAK). This kit can be personalized to the respective soldier and can therefore be equipped with individual medications needed in case of an injury. This may be considered if data from the military were transferred to civil emergency settings.

Rescue times and implication for the health care system

Given that several studies report that antibiotic prophylaxis reduce the infection risk of open fractures [20, 21], the prehospital application of antibiotics is likely to reduce the infection rates in open fractures in general [9]. As aforementioned, the use of prehospital antibiotics in the civil emergency setting is considered as safe and can easily be performed by health care professionals [16]. An implementation in modern rescue systems could thus easily be done and is likely to be necessary to collect the data needed to prove or refute the findings of this review.

The average rescue time for a severely injured person in Germany varies from 65.1 ± 37.3 minutes for big cities to 72.8 ± 42.4 minutes for small cities and 63.3 minutes if only penetrating traumata are considered [22]. Another study revealed 68.7 ± 28.6 minutes as the average rescue time in Germany for severely injured patients [23]. However, all these times are exceeding the maximum 60 minutes from incident to antibiotics that has been shown to be associated with a beneficial outcome as indicated by Lack *et al*. [4].

One review discussing the pre-hospital care of orthopedic injuries, pointed out that there is no need for pre-hospital antibiotic in a civilian setting due to the short rescue times of less than 60 minutes [9]. But as shown above and further by Lack *et al*. [4], most of the severely injured patients in civilian emergency settings in Germany and the USA, for instance, will not arrive at the hospital within an hour post-incident. All these patients could thus potentially benefit from a pre-hospital antibiotic prophylaxis.

There is a high variation of rescue times all over the world as can be seen in Figure 5. In the Netherlands, for instance, severely injured patients arrive in the hospital within a median time of 53.8 ± 28.6 minutes after incident [23]. In South Africa, the median time from incident to hospital for trauma patients was 45 minutes with an interquartile range from 36-63 minutes [24], whereas for traffic accidents in the US, the rescue time was indicated to be 44 minutes (interquartile range from 32 to 61 minutes) [25]. Furthermore, in the urban Scandinavian setting, the median total rescue time for patients with penetrating injury was assessed as 28 minutes (interquartile range 27-48 minutes) [26]. The high variation of pre-hospital rescue times may be the result of the different rescue systems such as “load, go and treat” in contrast to “stay and play”. Also, the different grades of severity and injury patterns compared above may contribute to the rescue time differences. The rescue times mentioned above can still give an approximate assessment of rescue times in different countries. Independent of the rescue system there are always patients arriving at the hospital in a time >60 minutes and in most cases 60 minutes are within the interquartile range; for those patients, the pre-hospital administration of antibiotics is likely to be associated with a better outcome.

Pre-hospital antibiotic prophylaxis could be implemented in a “load, go and treat” system or a “stay and play” system for most of these cases, meaning that there is no need to change the actual rescue system. It would only need the implementation of the pre-hospital antibiotic prophylaxis. This could be implemented in the on-scene treatment, for instance, if the local EMS follows a “stay and play” rescue system. Furthermore, pre-hospital

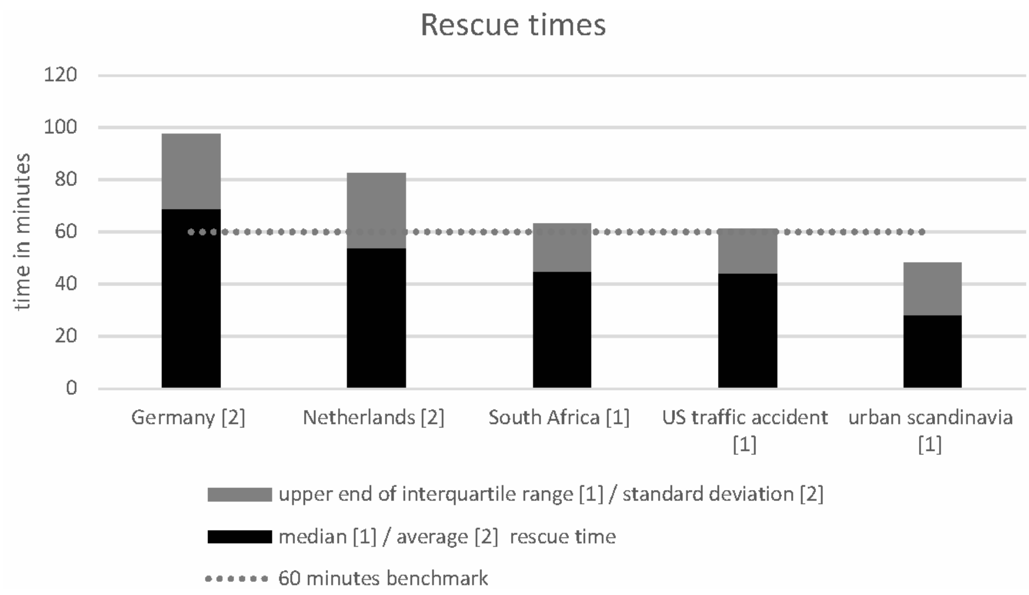

Figure 5. Comparison of rescue times showing the median [1] or average [2] rescue time (time from incident to arrival in the hospital) and the upper end of the interquartile range [1] or standard deviation [2]. Data from Timm, Maegele [23] (Germany and Netherlands), Möller, Hunter [24] (South Africa), Hu, Dong [25] (US traffic accident) and Bagher, Todorova [26] (urban Scandinavia).

antibiotic prophylaxis might be applied in any of the above-mentioned rescue systems if extended on-scene care is needed. In a "load and go" system, the prehospital antibiotic prophylaxis could be administered in the ambulance on the way to the emergency department.

This mini-review revealed that pre-hospital antibiotic prophylaxis is very likely to reduce the risk of infection for open fractures and is also likely to reduce the risk of infection for penetrating injuries in general. As stated in the introduction, lower infection rates are also important in terms of the combat of rising antibiotic resistances which would make the reduction of the amount of applied antibiotic compound essential. This could be done for example by preventing wound infections. If pre-hospital antibiotic prophylaxis is used, it is likely to lower the infection rates and therefore, the cases of patients needing extended antibiotic treatment of wound infections. In addition, an article from the Universitätsklinikum Carl Gustav Carus Dresden, Germany showed that single-shot antibiotics were virtually as effective as conventional preoperative antibiotics with a far less pronounced risk of subsequent antibiotic resistances [27]. This could also mount in lowered rates of antibiotic resistances, if pre-hospital antibiotic prophylaxis were used under the premise of rationale and responsible pre-hospital SAP. Hence, further research is necessary regarding pre-hospital antibiotic prophylaxis for penetrating trauma in general. Furthermore, a pre-hospital administration of antibiotics for open fractures should be added as a strict recommendation instead of an optional annotation to the guidelines.

Limitations

The presented mini-review has several limitations. Most importantly, the total number of articles as well as the numbers of patients included in respective surveys were relatively small. Furthermore, the three included studies focused on different injury patterns and defined different endpoints (48 hours without infection [17], clinical outcome after 90 days [4] and after 6 months [18]). Hence, studies with larger cohorts and comparably defined conditions including outcomes are needed to support the presented findings.

CONCLUSION

In case of open fractures there is evidence for pre-hospital SAP reducing the infection rates. It is likely that the benefits of prehospital SAP for open fractures can be transferred to many types of penetrating injuries in general. The usage of pre-hospital

SAP is considered safe according to one study. Larger studies with bigger cohorts, however, are needed to further support these findings.

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ETHICAL STATEMENT

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare that no conflict of interest exists.

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