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Cover Page Footnote

Many thanks are due to Dr. Aula Abbara of the Imperial College, London for providing the anonymized details for the previously unreported patient case.

Managing a conflict-related, open fracture with drug-resistant infections: The case of a wounded Syrian refugee in the Hashemite Kingdom of Jordan

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ABSTRACT A critical appraisal and clinical application of Uruc V, Ozden R, Duman IG, Dogramaci Y, Yengil E, Karapinar S, Karakus A, Kalaci A. Major musculoskeletal injuries and applied treatments in the current conflicts in Syria. *Acta Medica Mediterranea*. 2014;30(3):637-644.

Keywords: *infection, injury, fracture, open fracture, antimicrobial resistance, antibiotic resistance, drug resistance, refugee, conflict-related injury*

Clinical Context

Ahmad ash-Shamsi [pseudonym], a 30-year-old, male patient from Syria was admitted to a hospital in The Hashemite Kingdom of Jordan ("Jordan") with multiple, penetrating abdominal wounds and a fracture of the left femur. Mr. ash-Shamsi had reportedly been injured as the result of a barrel bomb striking the building he was staying in. Following the injury, the Mr. ash-Shamsi was stabilized and transferred to the hospital in Jordan; it is unclear if the patient received any prophylactic antibiotics or even what immediate interventions were administered.

Upon arrival at the hospital, the Mr. ash-Shamsi was febrile, hypotensive and was noted to have peritonitis. Fluid resuscitation was initiated, and the patient was given ceftriaxone and metronidazole before being taken into the operating theater. During the operation, Mr. Hussein underwent a washout of the abdomen, bilateral urostomies, a colostomy, and a washout of the left hip wound. Traction was applied to the left femoral fracture while the wound to the left hip was left open. Mr. ash-Shamsi continued to receive ceftriaxone and metronidazole but remained febrile at 48 hours, and then underwent a second washout of the abdomen. Given that Mr. ash-Shamsi remained febrile post-operatively, his antibiotics were escalated to tazocin and, subsequently, meropenem; he also received intermittent doses of gentamicin.

Despite the escalation in his antibiotic regimen, the patient continued to exude pus from the abdomen and the left hip wound. A wound swab from the abdominal pus grew a *Pseudomonas* species which was resistant to: ampicillin, aztreonam, cefixim, ceftazidime, ceftriaxone, cefuroxime, clindamycin, amikacin, erythromycin, ofloxacin, and piperacillin/ tazobactam; the same isolate was sensitive to ertapenem and levofloxacin. A wound swab of the left hip isolated an *E. Coli* species that was resistant to: amikacin, ampicillin, azithromycin, aztreonam, cefixime, ceftazidime, ceftriaxone, clindamycin, ertapenem, erythromycin, piperacillin/tazobactam; the same isolate was sensitive to levofloxacin.

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After multiple washouts and a prolonged course of meropenem, the patient started to improve. The team of medical providers discussed when and how to fix the infected left femoral fracture, as the risk of infection to any metalwork inserted would be high.

According to discussions between Mr. ash-Shamsi and his care team, he exhibited no health concerns before the barrel bomb incident. Having come to Jordan as a refugee, however, Mr. ash-Shamsi was liable to either be repatriated to Syria or sent to Zaatari Refugee Camp following his treatment. Given that the Mr. ash-Shamsi's family members were still in Syria, he was looked after by the nurses in the hospital in Jordan.

In discussions, Mr. ash-Shamsi specifically expressed his concern that he would become dependent during and after his recovery given the extent of his injuries. He had reportedly always been slim but had lost a great deal of weight during his illness and had experienced muscle wasting due to being bed-bound. He, furthermore, had never married, and noted his concern about finding a partner given his potentially debilitating injuries.

Clinical Question

Is internal fixation an appropriate means of bone stabilization in patients with combat-related, open femoral fractures who are at risk of infection (particularly drug-resistant infections in the Eastern Mediterranean)?

Research Article

Uruc V, Ozden R, Duman IG, Dogramaci Y, Yengil E, Karapinar S, Karakus A, Kalaci A. Major musculoskeletal injuries and applied treatments in the current conflicts in Syria. *Acta Medica Mediterranea.* 2014;30(3):637-644.

Related Literature

The literature review for this critical appraisal was conducted via a large-scale search of the bibliographic database Embase. An initial pilot search utilizing the terms battle injury, wound infection, and Syrian Arab Republic (yielding 5 search results with 2 pertinent publications). Following the subsequent identification of archetypal publications concerning combat-related injuries and infections by the Infectious Diseases Clinical Research Program ("IDCRP") of the U.S. Uniformed Services University, applicable index terms were collected and serially tested in Embase. Narrow terms were then optimized for broader results and reduced article-loss by conversion to overarching, hierarchical Emtree (Embase subject heading) terms. The final result was a query of Embase incorporating the Emtree terms Injury, Infection, Antiinfective Agent, Drug Resistance, Drug Sensitivity, Middle East, North Africa, Djibouti, Pakistan, and Afghanistan, with associated Boolean terms. This search yielded an initial 1,279 results. Following a review for relevance of the results, and the subsequent incorporation of supplementary articles via a citation-led review of select articles, 56 articles were found pertinent, and one primary research article was selected for critical appraisal.

Of the 56 articles found pertinent, five are particularly illustrative of the research concerning conflict-related injuries with open fractures, and infection by drug resistant organisms in the Eastern Mediterranean region. These three will be briefly summarized below, in ascending relevance, before the selected critical appraisal.

1. Teicher et al., 2014 conducted a retrospective chart review of refugee patients treated for war wounds in the Medecins Sans Frontieres ("MSF"; "Doctors Without Borders") surgical hospital in Amman, Jordan. The article reported that 74% (45/61) of Syrian patients suspected of infection had at least one positive culture, that 23% (10/43) of applicable isolates were *P. Aeruginosa*, that 19% (8/43) were *E. Coli*, and that 69% (31/45) of patients with confirmed infections were positive for multidrug resistant organisms. The study, however, does not specify injury type nor assess treatment modalities.¹

2. Herard, Boillot, & Fakhri, 2017 conducted a retrospective chart review examining the bone cultures of 1,653 patients from Iraq, Syria, Yemen, and Gaza who were treated at the MSF facility in Amman, Jordan. In looking at the occurrence of infection, the article found that infection rates were 86% (850/991) among patients who received debridement and external fixation and 46% among the 167 patients who received internal fixation. The article also ultimately advocated for the use of routine bone cultures, noting that



46% of 167 patients who did not display any signs of infection were found to be infected. The article is extensive, but as it focuses on patients of multiple nationalities and conflicts and bone cultures (which the case patient did not receive), the findings are not directly applicable.²

3. Keeling et al., 2008 conducted a retrospective study that ultimately encompassed of 45 open, combat-related tibial shaft fractures in 43 U.S. military personnel that were managed via external fixation ring. The article found that use of the external fixation ring resulted in a low rate of complications (only 8% of tibiae developed deep infection, and only 8% demonstrated noninfected nonunion) and a high rate of fracture union (only 220 +/-67.2 days to union). This study, however, focuses solely on tibial fractures in a U.S. military patient population and did not allow comparison of fixation types.³

4. Mack et al. 2013 conducted a retrospective case assessed 41 patients with combat-related, open, femoral fractures. The study reported that 83% (34/41) of patients were managed via cephalomedullary or reconstruction nails, and that of the 39 patients who had at least two years of follow-up, the mean time to union was 5.1 months, reoperation was required in 56% (22/39) of patients, wound infection occurred as a complication in 31% (12/39) of patients, and heterotopic ossification occurred as a complication in 26% (10/39) patients. The study, however, focused on a U.S. military patient population, and assessed cephalomedullary nails rather than external fixation as a treatment modality.⁴

5. Bennett et al. 2015 conducted a retrospective case series specifically on combat-related, femoral fractures in UK military personnel. The study found no statistical correlation between fixation methods and poor outcomes, and reported that one of its four patients developed an E. Coli infection (analogous to the case patient). The overall patient population, however does not match the patient case well, and the sample size only entails 47 patients who were selected over ten years.⁵

As all of these studies generally demonstrated the same level of evidence (Level IV), the factors that set the critical appraisal article apart are its larger sample size, its examination of internal and external fixation outcomes alike, and its unique demographic relevance to the case described above (further elaborated upon in the "Clinical Application" section below).

Critical Appraisal

The selected article by Uruc et al. is a retrospective case series (chart review) that was published in 2014 in the peer-reviewed journal *Acta Medica Mediterranea*, thereby constituting level IV evidence per the Oxford Centre for Evidence-Based Medicine's 2011 guidelines.

In brief, the study examined the records of 579 Syrian civilians who were injured in the ongoing civil and regional conflict in Syria and presented subsequently for treatment at the Mustafa Kemal University Hospital between December 16, 2011 and August 17, 2013. Criteria for inclusion entailed being a Syrian civilian who received treatment for musculoskeletal injury at the hospital during the aforementioned period. Patients seeking elective treatment were excluded from the study.

Before further elaboration, one can summarize the study's strengths as the following: 1) it offers explicitly stated inclusion and exclusion criteria, 2) it incorporated eligible subjects in a consecutive and comprehensive manner within the delineated time period (limiting inherent selection bias), 3) it ultimately encompassed a large sample size, 4) it reported the demographics of the subjects in terms of age and sex, 5) it clearly reported subjects fracture subsets and clinical treatments, 6) the treatments considered are feasible in most conventional, surgical settings, and 7) its mathematic analysis (while limited) was appropriate to its findings.

The study's weakness can be summarized as follows: 1) the standards for clinical presentations and outcomes were not explicitly defined, 2) there is no distinction between microbial infection, colonization, and contamination, 3) the methodology for microbial analysis was not explicitly stated (neither the swab type nor location or time were identified), 4) intervention surgery protocols were not delineated enough to assure standardization, and 5) comparison between external fixation and internal fixation patients is not possible due to the reported difference in patient populations (vis-a-vis evacuation delays and degree of wound contamination).

When examined at greater length, one can note that while inclusion and exclusion criteria are explicitly stated in this study, they are not always robust or detailed. Notably, there is no explication of how the Syrian nationality of subjects was confirmed or previously recorded. Moreover, the conflict-related nature of the injuries was ascertained solely via respondent surveys, and while the term



“civilian” is used throughout the paper, there is no means by which to confirm that the subjects were in fact noncombatants. As many of these details are logistically exacting to ascertain in a stable environment, much less a conflict environment, however, and likely have little impact on clinical outcomes, they are not deep impairments of the study’s credibility.

As a retrospective case series in general, this study constitutes an observational examination of a patient group without the benefit of a comparison via a control group. The study, therefore, does not employ randomization or blinding, cannot be subjected to quantifications of absolute risk, relative risk, or odds ratios, and does fall victim to particular biases.

Notably, since the study considers patients from the Syria that were able to reach Turkey for treatment, the study does fall victim to a degree of selection bias (despite consecutive and complete selection within the time period). As a result, the subject population may not be representative of all Syrian patients with combat-related open fractures, much less general patient populations with the condition. Since, the study was conducted on the basis of a chart review, the selection bias constitutes a severe limitation. Moreover, the authors explicitly state that external fixation was a treatment modality preferred in patients with greater evacuation time and wound contamination, identifying a source of indication bias in comparing the infectious outcomes of external versus internal fixation.

Nothing can be said of potential funding bias, as the authors did not report or deny potential conflicts of interest in the body of the paper.

Clinical Application

This critical appraisal specifically aims to assess Level IV evidence as a basis for clinical decision-making in vulnerable patient populations. Due to the nature of medical care and research in conflict settings, and specifically the management of combat-related injury, the body of existent literature is composed predominantly of retrospective case series (Level IV evidence), and demonstrates a notable dearth of prospective studies, much less case-control studies, cohort studies, or randomized, clinical trials.

The paucity of such research is further exacerbated when looking for combat-related injuries in: 1) noncombatant and refugee populations, 2) a defined geographic region, and 3) confluence with drug-resistant organisms. It is imperative, therefore, that researchers and clinicians be familiar with the means by which to appraise the validity and utility of case series if they are to serve populations exposed to conflict. This skillset is especially important given the wealth of guidelines and literature reviews in the field of conflict wound management that are derived from these retrospective case series, which otherwise mask the validity of their constituent studies in a composite analysis.

In these conditions, “best available/applicable” evidence often replaces “best” evidence. This appraisal, therefore, is meant as an exercise in appraising and interpreting what limited evidence exists to the benefit of profoundly vulnerable patients such as Mr. ash-Shamsi.

Regarding the internal validity of the selected study, the authors primary conclusion appears to be in correspondence with the given results. Despite the weaknesses addressed above vis-à-vis the study’s design, the ultimately low rate of infection (2.7%; 14/514) among patients with 3a open fractures who did not have delayed evacuations, presented with limited wound contamination, and received aggressive debridement, irrigation, and internal fixation, raises the possibility of internal fixation being a safe therapy for the noted fracture subtype (which is due to high-energy injuries associated with extensive soft tissue damage, traumatic amputations, or segmental fractures of >10 cm in length) and subpopulation.

The external validity of this study in reference to above-noted patient case is prominent and multifold in terms of demographics. Not only does this study focus on a predominantly male population (89.8%; 520/579) with a mean age of 30 (precisely matching the above-noted patient case), but 78% (668/766) fractures were open, 20% (131/668) of the open fractures were of the femur (sharing the same anatomic location as the patient), 77 members of the overall patient population developed infections, and the most commonly isolated microbial



organisms were *Pseudomonas Aeruginosa* and *Escherichia Coli* (precisely matching the two multidrug-resistant organisms isolated from the case-patient).

The external validity of this study falls short in the subjects' mechanisms of injury and the category of patients who received internal fixation. Whereas Mr. ash-Shamsi suffered what can be characterized as a blast or explosive injury (likely with secondary, tertiary and quaternary burn, crush, and pressure damage), the majority of patients examined in this study reported "gunshot" as the primary mechanism of injury. Among the male patients, 80% were injured via gunshot and only 6.3% were injured via "explosions." Additionally, while the case patient's femoral fracture may apply to the 3a category delineated above, the duration of his evacuation from Syria is unknown, as was the degree of contamination in his infected fracture.

In one subset of the selected study, 21 patients with grade 3a open fractures, delayed evacuation (> 6 hours), and contaminated injuries (undefined) were treated with external fixation, continuous debridement, and irrigation every 48 hours. This patient group saw wound infections persist in 43% (9/21) of its members, 5 (56%) of which later required above-the-knee amputation and 4 (44%) of which later received below-the-knee amputation. Yet, without knowing the subtypes of these patients' fractures, lacking the evacuation and contamination measures of the case patient, and noting the small sample size of this subpopulation, these values would not have been applicable to the clinical care of the case patient.

Ultimately, given that Mr. ash-Shamsi was part of an international medical mission, the knowledge of his medical record is fragmentary, and his ultimate outcome is unknown. This critical appraisal was conducted for the purpose of applying lessons from his case for the benefit of future patients.

Given the patient's social concerns (separation from family support structures, the potential for reduced independence, and the fear of not finding a partner to marry), the priority for this patient would be in mitigating his post-operative disability. Emphasis would be focused on selecting the treatment modality with the lowest rate of infection, reoperation, and amputation, and the highest rate of fracture union and subsequent limb functionality. A discussion would need to occur with Mr. ash-Shamsi informing him of the treatment options, the incumbent risks, his expected time as an in-patient, and his likely outcomes. Such a discussion would enable him to plan for himself and his family members and begin to seek out the resources necessary to ensure a safe future.

Ultimately, the paper selected, while of great apparent demographic relevance, does not enable the author of this critical appraisal to undertake that conversation or to recommend any treatment option over another. Rather, it may caution against the use of Level IV evidence, even despite the presence of apparent external relevance, as a basis for either clinical decisions or composite literature reviews. In looking at this critical appraisal's clinical question, the selected paper was only able to answer that a subset of patients with ideal evacuation and contamination conditions may benefit from internal fixation. The future outcomes of patients like Mr. ash-Shamsi presented in this critical appraisal will rely on the implementation of robust follow-up studies with broader, comparative scopes.

Learning points:

1. Retrospective case series take on diverse and sometimes divergent design methodologies. These studies are well suited to the environments of conflict environments enabling flexible study designs and necessitating only minimal time and financial investments. The weakness of these studies arise when: 1) comparison groups are not, or cannot, be utilized, 2) medical records do not enable the inclusion of adequate detail to ensure standardization, and 3) the correlation of interventions and outcomes occurs in specific patient subpopulations, limiting extrapolation to broader groups.
2. In assessing retrospective case series, the clinician should look to studies with clear inclusion and exclusion criteria, detailed definitions of disease states and clinical outcome measures, and carefully selected comparison groups where possible; literature reviews should focus on such studies as well.



3. Contemporary publications on the surgical management of combat-related, open fractures demonstrate a significant knowledge gap in the comparison of fixation devices, particularly when also considering preexisting infections and drug resistant infections. This topic will likely be of exceptional importance in the treatment of refugee and conflict-afflicted populations.

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