MENTORS IN ORTHOPEDICS

FIRST EXPERIENCES IN DELAYED RECONSTRUCTIVE TREATMENT OF WAR INJURIES FROM THE UKRAINE CONFLICT . A RETROSPECTIVE DATA ANALYSIS FROM 2018 - 2022 FOCUSING ON MULTI DRUG RESISTANT BACTERIA AND SPENT RESOURCES

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SUMMARY

Background: Management of chronic war injuries is complicated by a temporal shift in microbial flora from gram-positive contaminants to multidrug-resistant (MDR) gram-negative organisms. In patients with complex blast or gunshot trauma, identifying occult infectious foci and assessing bone fragment viability are critical for successful reconstructive surgery and the prevention of hardware-related infections.

Objective: This study evaluates the prevalence of MDR bacterial colonization in Ukrainian patients with chronic conflict-related injuries and assesses the utility of advanced nuclear medicine imaging in guiding surgical debridement and treatment planning.

Key Points: Among 26 patients treated over a four-year period (mean 6.9 months post-injury), 81% demonstrated MDR colonization. Microbiological analysis of 1,838 samples identified 4MRGN in 46% and 3MRGN in 58% of the cohort. To refine surgical strategy, anti-granulocyte antibody (AGA) SPECT/CT was utilized in 10 cases to localize infection around retained fragments, while 18F-sodium fluoride (Na[18F]F) PET/CT was employed in four cases to identify avital bone segments. These hybrid imaging modalities provided precise functional and anatomical data, facilitating the targeted removal of necrotic bone and infected foreign bodies that appeared clinically quiescent.

Conclusion: High rates of MDR colonization in chronic war trauma necessitate rigorous screening and specialized diagnostic protocols. Integrating AGA-SPECT/CT and Na[18F]F-PET/CT into the preoperative workup allows for the definitive identification of infectious reservoirs and non-viable bone, optimizing the biological environment for subsequent internal fixation and bony reconstruction.

KEYWORDS

War Injuries; Osteomyelitis; Multidrug Resistance; Single Photon Emission Computed Tomography Computed Tomography; Positron Emission Tomography Computed Tomography

INTRODUCTION

The conflict between Ukraine and Russia began several years before the start of the war between those two countries. Both before and after the start of the war, patients from Ukraine were also treated in other countries. The Federal Republic of Germany also decided to make a humanitarian contribution to the care of the injured from this conflict and to treat patients within the Federal Republic of Germany. As part of this pledge, 26 patients received medical care at the German Armed Forces Hospital Ulm from 2018 to 2022. These were not newly injured people, but patients who had already been treated in Ukraine over a longer period of time and generally had chronic wounds and injuries.

Many studies have shown that the bacterial spectrum in war wounds changes over time. Initially, contamination with gram-positive skin germs with no or a very low proportion of MRSA can be detected [10],[12],[17], while this spectrum then changes after just a few days and the gram-negative germs predominantly colonise [16],[17]. In many cases, multi-resistant germs are also detectable. For example, Campbell at al. showed that of 2699 injured soldiers from Afghanistan and Iraq, an infection was detected in 34% (n=913) of their injuries in the hospitals back in the USA [4]. Of these 913 patients, 27% (n=245) had an infection with multidrug-resistant bacteria, which corresponds to an overall rate of 9.1% of the 2699 injured soldiers. After repatriation, 1018 patients were treated in the intensive care unit and 19% (n=193) developed an infection with multidrug-resistant bacteria. On the way to repatriation, 391 patients were treated in the intensive care unit at the hospital of the American armed forces in Landstuhl/Germany. Here, 11.4% had an infection with multi-resistant germs. The authors were also able to show that pneumonia, soft tissue infections, osteomyelitis and urinary tract infections accounted for the highest proportion of infections with multi-resistant germs. A French study of 28 patients with war injuries showed that 25% were infected with multi-resistant germs, while 57% were found to have multi-resistant germs [1].

Modern hybrid scanners, which combine molecular imaging using positron emission tomography (PET) and single photon emission tomography (SPECT) with morphological radiological methods such as computed tomography (CT) or magnetic resonance imaging (MRI), allow precise functional and anatomical localization diagnostics such as PET/CT, PET/MRI or SPECT/CT in a single examination.

Granulocyte or leucocyte scintigraphy with SPECT/CT has high sensitivity and specificity for peripheral bone infection with hardware in situ [6].

Skeletal scintigraphy with 99mTc-labelled bisphosphonates is often one of the first diagnostic steps in MSK infection [15]. As a three-phase scintigraphy, it can be used to exclude infectious pseudarthrosis, as its sensitivity of 92-95 % is excellent, but its specificity of 18-33 % is not sufficiently satisfactory. The low specificity can be increased to 72-84 % in combination with granulocyte antibody scintigraphy as part of a staged diagnosis [11].

In three-phase skeletal scintigraphy, the uptake of the 99mTc complexed with a diphosphonate used depends on blood flow and bone turnover. In the mineralization phase, a typical accumulation pattern can be observed during fracture healing. Prolonged persistent tracer accumulation in the fracture region during the mineralization phase indicates the development of non-union.

18F sodium fluoride (Na[18F]F) is a positron emitter and is used as a radiopharmaceutical in PET/CT. It has a similar pharmacokinetic behavior to the 99mTc diphosphonates used in gamma camera skeletal scintigraphy (SPECT). However, Na[18F]F-PET/CT has the advantage of a higher spatial resolution and specificity compared to skeletal scintigraphy. As a dynamic examination, Na[18F]F-PET is mainly used clinically in the vitality diagnostics

of bone grafts. A reduced fluoride influx in the perfusion phase indicates that the graft is no longer vital [18]. The dynamic examination approach in PET/CT is currently not widely used because it requires the drug to be produced in a PET radiopharmacy according to GMP (good manufacturing practice) guidelines.

The aim of this paper is to give an impression of the extent of colonisation and infection with multidrug-resistant bacteria in this patient group and to show which diagnostic tools were necessary or recommended in order to be able to draw up a successful treatment plan for these patients. However, the aim of this publication is also to specifically address other clinics and doctors who were also involved in the treatment of patients from this conflict, as it is hardly possible to draw relevant conclusions from the patient numbers of a single clinic. However, the large total number of patients treated in this conflict should make this possible. And it is precisely this fact that is one of the aims of the WAIOT to collate the results from septic traumatology in order to finally increase the evidence in this field.

METHODS

Between 2018 and 2022, a total of 26 Ukrainian patients were admitted to and treated at the Department of Trauma Surgery and Orthopaedics at the German Armed Forces Hospital Ulm. The patients came to us an average of 6.9 months after the injury (range 1 - 74 months). The patients had multiple injuries and remained in our care for an average of 118 days (range 13-491 days). In most cases, the number of previous operations as well as the type of previous operation was unclear, as the documentation given to the patients was often incomplete.

Microbiological examinations

Patients underwent a variety of microbiological tests during their treatment at our clinic. All patients underwent MRE screening on admission, as is mandatory in our clinic. Patients were also repeatedly subjected to MRE screening during the course of their treatment in order to either be able to stop isolation or to fulfil the requirements of a rehabilitation facility before treatment was accepted. Wound swabs and tissue samples were also taken during surgical procedures. As the patients were also treated during the coronavirus pandemic, numerous SARS-CoV-2 tests were also carried out using PCR methods.

Nuclear medicine examinations

In most cases, the patients had multiple injuries. In many cases there were chronic wounds and older fractures. Anti-granulocyte antibody (AGA) scintigraphy and SPECT/CT examinations were used in these cases in order to be able to reliably distinguish between Post-traumatic osteomyelitis (PTO), also known as ‘fracture-related’ osteomyelitis with increased AGA uptake and non-specfic changes in the case of ambiguous wound conditions. For treatment planning, it was also important to know which fragments of the fractures were avital in order to remove them and thus eliminate a possible reservoir for bacteria. For this purpose, we used 18F sodium fluoride (Na[18F]F) PET/CT examinations to detect avital bone fragments.

RESULTS

A total of 2095 microbiological tests were carried out on our patients. These included 257 coronavirus PCR tests, which are not listed below.

Of the remaining 1838 microbiological tests, most were due to MRE screening. These were carried out on all patients both on admission and repeatedly during the clinical course. There was not always a hard indication for this. In some cases, MRE screenings were carried out to see whether isolation could be cancelled or before a planned transfer to a rehabilitation facility at the request of this facility. A total of 1050 swabs were taken as part of these screening examinations. Of these 1050 swabs, 68 were positive for 3 MRGN germs, 93 swabs were positive for 4 MRGN, 18 swabs were positive for MRSA and a further 6 swabs were positive for VRE. However, there is certainly also a selection bias here, as the majority of patients admitted were those who would have required the limited resources in Ukraine far more than average due to the military conflict. In addition to the MRE series, 314 wound swabs were taken. These resulted in the detection of 76 3MRGN and 104 4MRGN as well as 5 MRSA colonisations. Further 281 tissue samples were taken from our patients. This revealed evidence of 3MRG in 23 cases and 4MRGN in 54 cases. Urine was analysed a total of 23 times and 4MRGN was detected in 2 cases. There were 11 blood cultures, but in each case without evidence of multi-resistant colonisation. All other microbiological examinations (e.g. from the IVC but also unclassifiable samples) comprised a total of 159 examinations, of which a 3MRGN was detected in 7 cases, a 4MRGN in 6 cases and 1 VRE in one case. The results of our investigation are summarised in Table 1.

	MRE Screening	Swabs	Tissue Samples	Urine	Blood Cultures	Other
n	1050	314	281	23	11	159
3MRGN	68	76	23	0	0	7
4MRGN	93	104	54	2	0	6
MRSA	18	5	0	0	0	0
VRE	6	0	0	0	0	1

Table 1: Number of microbiological examinations and their results regarding multiresistant bacteria

In relation to the individual patients, 19% (n=5) had no evidence of multidrug-resistant colonisation. We succeeded in detecting colonisation with a 4MRGN pathogen in 46% (n=12), while in 58% (n=15) a 3MRGN pathogen was detected. Detection of MRSA (4%, n=1) and VRE (4%, n=1) was significantly less common. The number of microbiological examinations varied between 3 and 295 per patient, including patients in whom a maximum of 5 different 4MRGN pathogens were detected simultaneously in different wounds and anatomical regions.

In 10 of the 26 patients, an anti-granulocyte antibody (AGA) SPECT/CT scan was performed to identify centres of infection and to assess the extent of infection. Na[18F]F-PET/CT or three-phase bone scintigraphy was performed in 4 and 2 of the 26 patients, respectively, to detect avital bone in fractures or reconstructions as a possible reservoir of germs and subsequently remove them in a targeted manner.

To better visualise the value of these examinations, please refer to Figures 1 to 3. Figure 1 shows a photo of a patient. It shows multiple injuries to the lower extremities with many small, seemingly non-irritant wounds and treatment with an external fixator. Figure 2 shows the corresponding radiograph of the right lower leg with the knee joint. Multiple small radiopaque foreign bodies can be seen. Figure 3 shows the evaluation using anti-granulocyte antibody SPECT/CT. It is very easy to recognize which foreign bodies accumulate granulocytes in their surroundings. This corresponds to an infection. Many other foreign bodies do not have this accumulation and are therefore not infected.

Figure 1: Patient with multiple injuries to the lower extremities and multiple small wounds

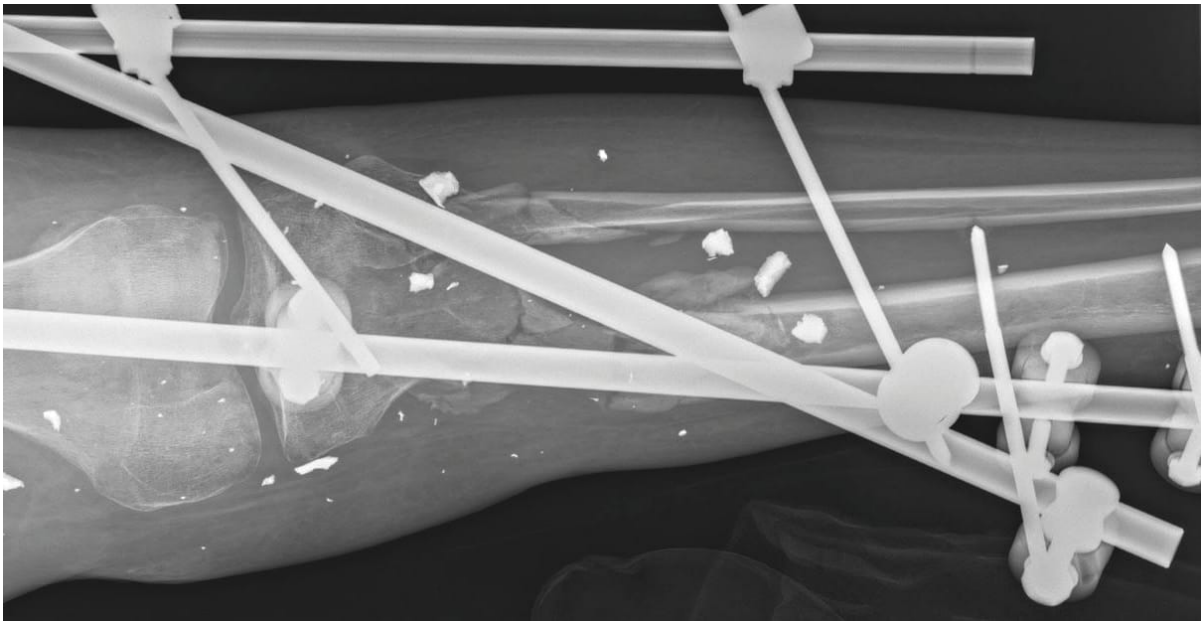

Figure 2: The a.p. radiograph of the right lower leg of the same patient showing multiple foreign fragments

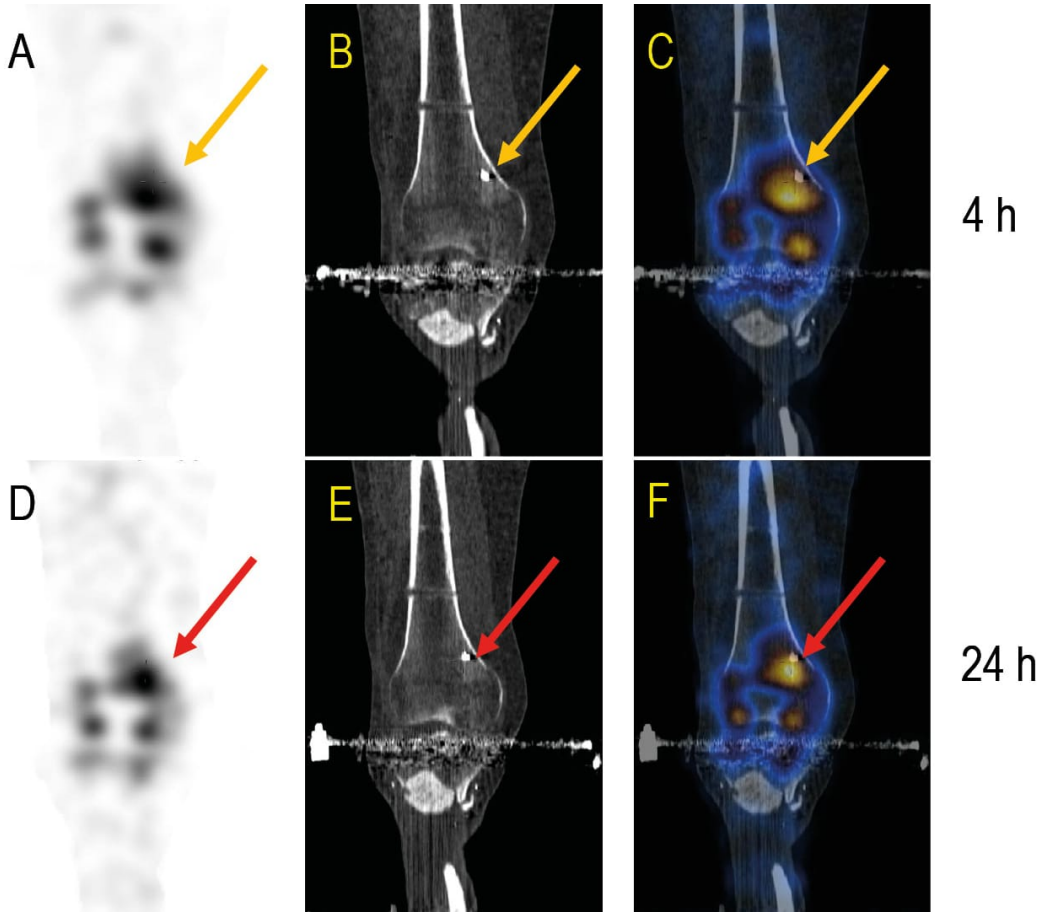

Figure 3: Anti-granulocyte antibody (AGA)-SPECT/CT presented an increased accumulation of granulocyte antibodies over time (orange arrows 4 h p.i., red arrows 24 h p.i.) in the medial femoral metadiaphysis adjacent to a radiopaque foreign body as an expression of an infected fragment. SPECT/CT with 99mTc-labelled granulocyte antibodies in coronal views of SPECT (A,D), CT (B,E) and fused SPECT/CT (C,F).

Figure 4 has a radiograph with a vascularised bone chip on the left humeral shaft on the left side, which shows no healing tendency months after reconstruction. On the right side of figure 4 the result using Na[18F]F-PET/CT. It can be clearly seen that the vascularised chip no longer has a bone metabolism. The chip is avital and must be removed. Cancelliosaplasty cannot be successful in this case.

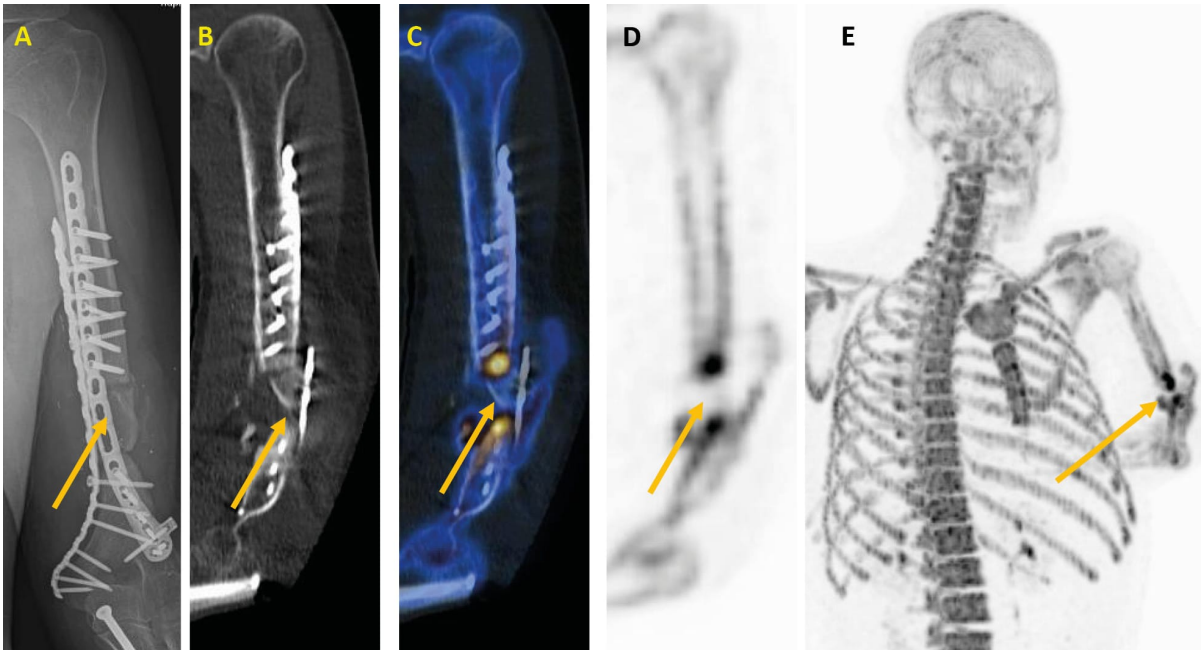

Figure 4: A radiograph of the left humerus showed a delayed union after bone chip implantation (orange arrow), corresponding Na[18F]F-PET/CT images (B-E) with coronal oblique view of the left humerus in the CT (B), fused PET/CT (C) and in the PET (D,E) present almost no tracer accumulation in the bone chip (orange arrows) in the mineralization phase in the sense of reduced to absent vitality and increased osteoblast activity at the fracture margins of the non-union with preserved vitality.

DISCUSSION

In the 26 patients we treated, we were able to detect multi-resistant germs in 81% (n=21). Since the patients we treated from Ukraine were not acute trauma patients but, on the contrary, exclusively patients with chronic injuries, our results fit very well into the picture of the available literature that an increasing multi-resistant colonisation and also corresponding infections exist the longer the patients have to be treated [4], although a gram-positive microbial flora can be detected in the wounds immediately after the trauma. Our patient population is therefore comparable with the Syrian children who were treated in Israel as refugees during Syria's civil war [7]. This study showed that a good 90% of the detected infections were found in the group of injured children, while only 10% of the infections were found in children without injuries. The authors regarded screening on admission as a very important tool for the early detection and targeted treatment of multi-resistant colonised patients.

Campbell et al. also found no evidence in the data of the patients examined for the theory that the war wounded could already be colonised with multi-resistant bacteria before their trauma in the military conflict [4]. The authors consider it very likely that the patients only acquired the multi-resistant germs in the course of the medical evacuation (MEDEVAC) and inpatient treatment. However, they see a clear correlation between the severity of injury and the risk of infection with multi-resistant germs. In view of the available literature, we also consider it unlikely that the injured soldiers were already colonised with multi-resistant germs at the site of the injury. It is much more likely that colonisation and, in many cases, infection with multi-resistant germs only occurs during the course of treatment. There also appears to be a correlation between the severity of the injury and the likelihood of infection with multi-resistant pathogens, as described by some authors [3],[4],[13]. In our

opinion, the patient clientele we examined corresponds to the patients Valentine et al. examined in their study [17], just at a much later point in time.

In an animal experiment with small, injected fragments, the authors were hardly able to find any relevant changes on the skin surface in many cases [2]. This is consistent with our experience that, particularly in the case of blast injuries, the skin over the blasted foreign bodies often shows no evidence of infection. In order to clarify the question of which injuries we should treat surgically first, imaging - especially nuclear medicine imaging - was of great value to us. Even though the initial screening and the first debridements gave us a good picture of the extent of the infections and the infected regions at an early stage, this imaging repeatedly gave us indications of unknown centres of infection or possible reservoirs for germs in avital bone areas.

Due to the high sensitivity and specificity for peripheral bone infection with hardware in situ granulocyte or leucocyte scintigraphy with SPECT/CT is recommended for this indication in current European consensus papers [5].

A study of 23 patients with suspected post-operative bone infection who underwent two-phase Na[18F]F-PET/CT showed a sensitivity, specificity and accuracy of 93 %, 100 % and 96 % respectively [9].

The dynamic Na[18F]F-PET/CT established at the German Armed Forces Hospital Ulm is excellently suited for vitality diagnostics of delayed-unions or non-unions and forms a basis for further treatment planning or redirection. The advantages of this tracer with unsurpassed image quality, shorter examination time and the possibility of dynamic examination including quantification are thus available for complex traumatological issues.

Complex blast or gunshot injuries can be optimally treated in a targeted and timely manner using additional complementary nuclear medicine molecular imaging modalities.

Modern nuclear medicine equipment with hybrid devices (PET/CT, PET/MRI, SPECT/CT) allows simultaneous morphological and functional imaging in a single examination.

Nuclear medicine diagnostic procedures are used in particular to rule out infection when previous diagnostics are inconclusive. Infectious pseudarthrosis may appear as both hyper- and atrophic pseudarthrosis on X-rays and can have varying degrees of biological vitality. The suspicion of infectious non-union must be consistently investigated in order to avoid delayed or inadequate treatment planning. Despite the lack of clinical evidence of an infection, bacteria can be detected in 44% of tissue samples from pseudarthrosis [14]. Nuclear medicine techniques such as granulocyte scintigraphy with SPECT/CT should therefore be used, especially in cases of pseudarthrosis due to infection.

CONCLUSION

We carried out a total of 10 anti-granulocyte antibody (AGA)-SPECT/CT scans and 4 Na[18F]F-PET/CT in our 26 patients in order to use these non-invasive techniques to detect unclear centers of infection and avital bone parts at an early stage and to be able to address them surgically in order to avoid subsequent infection of an osteosynthesis for bony reconstruction. This is because the multiple injured soldiers in particular had many injuries that were considered to have healed from the outside, which would not have been clinically recognized as the cause of an infection. From our point of view, patients with multiple and chronic injuries in particular benefited from these examinations, which are rather rare in normal clinical practice. Before bony reconstruction and the insertion of osteosynthesis material, detected centers of infection were eliminated and avital bone parts

removed. This certainly reduced the risk of further infections in the course of the treatment, even if our data do not have sufficient power to prove this with statistical certainty.

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