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INTERVIEW


Hiroyuki Tsuchiya

From rural Gunma to global eminence, Professor Hiroyuki Tsuchiya's journey in orthopedic surgery is marked by innovation and perseverance. His pioneering work in musculoskeletal oncology, the Ilizarov method, and infection control, particularly the development of iodine-coated implants, showcases his inventive approach. Tsuchiya's philosophy—"*Dream, dare, and do*"—and his reflections on life's essence reveal a mentor who values cheerfulness, hard work, and gratitude, inspiring the next generation of orthopedic surgeons.

: Can you tell us about your background? Where were you born and raised?

Hiroyuki Tsuchiya (H.T.): I was born in Gunma Prefecture, which is located about 100 km northwest of Tokyo. I'm not sure if you're familiar with Japanese geography, but that's where I spent my formative years until I was 19. I completed my elementary, junior high, and senior high school education there before moving on to university.

: Where did you attend university?

H.T.: I attended Kanazawa University in Ishikawa Prefecture. It's about 400 km west of Tokyo, facing the Sea of Japan, with the Korean Peninsula on the opposite side. Kanazawa University is one of the oldest universities in Japan, with a history spanning over 150 years. In fact, it's probably the third oldest university in the country.

: Why did you choose this particular university?

H.T.: I chose Kanazawa University for its medical school. At that time, the university was located within a castle, which made for a beautiful setting. The combination of its excellent medical program and the stunning location made it an appealing choice for me.

: What motivated you to pursue medicine?

H.T.: To put it briefly, my decision to study medicine was deeply personal. When I was in high school, my father passed away from liver cirrhosis, likely due to alcoholism rather than viral causes. I felt incredibly frustrated by the lack of treatment options available for his condition. This experience ignited my desire to become a doctor and find a cure for liver cirrhosis. Interestingly, while that was my initial motivation, I ultimately became an orthopedic surgeon rather than a physician specializing in liver diseases. Time changes people.

OVERVIEW

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The World Association against Infection in Orthopedics and Trauma (WAIOT):
Continuing the fight to the musculo-skeletal infection silent epidemic.

Since its conception, WAIOT was designed to be an open, free and inclusive scientific association, aimed at bringing together all professionals interested in musculo-skeletal infections (MSIs).

Free of charge, easy to access, open to the participation of experts from different disciplines and with a worldwide perspective, WAIOT is quite unique in the orthopaedic and trauma scientific associations' panorama.

Founded in Vienna, in May 2017, with a relatively low-budget and manly relying of the voluntary, free-of-charge work of its Members, WAIOT now counts more than 2,400 associates from 110 Countries.

Among the main missions of WAIOT is to raise knowledge and awareness regarding the largely neglected and underestimated problem of MSIs among health professionals and governmental authorities and institutions.

In line with this mission and continuing the fruitful cooperation between WAIOT and the MO Journal, this **3rd Special Issue** brings us into one of the most complex and challenging fields of bone and joint infection management: **war-related musculo-skeletal infections**. Conflicts and low- and high-intensity confrontations around the world, which many thought were going to be a thing of the past, are on the contrary back with renovated intensity and multiplied potential risks. Technological advancements and new military strategies and doctrines, which are now opening the way even to nuclear superpowers and blocs to confront themselves in "regional" military operations, are disclosing new and extremely dangerous war scenarios.

Two papers in this Special Issue specifically address the impact of multi-resistant bacteria and their biofilms in war-related musculo-skeletal infections; the first article, reporting a detailed literature review, teaches us the actual risk of **highly multi-resistant bacteria spreading in and from the battlefields**, even if the exact reason(s) of the high rate of antibiotic resistance in conflict zones remains insufficiently understood and investigated. The second paper, which reports the clinical experience of the **German Armed Forces Hospital in Ulm, Germany,** illustrates some of the complicated injuries suffered in the ongoing conflict in eastern Europe with their related costs and the possibility offered by some of the most recent technologies to improve war-related MSIs management.

This Special Issue further offers an interesting study by **Prof. Alizadeh and co-workers** from **Azerbaijan**, detailing the **histological aspects of knee septic arthritis with and without previous steroid injections**. The occurrence of aspecific inflammatory findings and up to 1/3 culture negative infections is well in line with the findings reported in the MO_Journal 2023 WAIOT Special Issue, highlighting the need for chemical antibiofilm pre-treatment methods to more effectively culture bacterial aggregates in fluids of *(cf. "Bacteria living in biofilms in fluids: can we improve our cultural examination of synovial and other organic liquids ?" MO Journal, WAIOT Special Issue, August-July 2023).*

Egypt is currently the number one Country for number of WAIOT Members. Their interest in musculo-skeletal infections is well reflected by what we learn for the nicely documented paper of **El-Rosasy and co-authors**. According to their **systematic review and meta-analysis**, conducted to evaluate the prevalence of **orthopedic surgical site infection in Egyptian hospitals,** the authors find an estimated incidence of surgical site infection ranging from 12.5% to 32.3%, which is among the highest in Africa. While several avoidable risk factors are advantageously identified by the authors, their findings also appear of value for healthcare providers and governmental institutions, prompting the authors to suggest a "*multicenter surveillance study, on many homogeneous Orthopedic cases with larger sample size and longer duration to allow for meaningful comparisons between different Orthopedic conditions and hospitals*."

From Egypt to the Far East, **Prof. Takeshi Morii and Prof. Hiroyuki Tsuchiya** bring us into the history and perspectives of a n**ationwide analysis on surgical site infection and in tumor endoprosthesis in Japan**. The complexities, the advantages and disadvantages of each registration method are evaluated and discussed. The need for a prospective registration system for tumor endoprosthesis complications is finally outlined, in order to achieve a better control and a mitigation of the still unacceptable high rate of septic complications after oncological surgery, even in the best centers of the world.

However, the contribution of **Professor Tsuchiya** does not end with this scientific paper. **As the incoming WAIOT President**, he also opens the WAIOT Special Issue with an inspiring and full of contagious enthusiasm **Interview**.

Finally, after the **3rd WAIOT Annual Congress, organized by Prof. Joseph Benevenia in Miami, FL, USA,** the next WAIOT President announces the **4th WAIOT Congress, which will be held from September 5 to 6, 2025 in the beautiful city of Yokohama, Japan**, hosted by **Professor Yutaka Inaba, Congress President and Chairman of the Department of Orthopaedics at Yokohama City University**.

After this too long Editorial, wishing you a good lecture of the 2024 WAIOT MO_Journal Special Issue, I cannot avoid inviting all of us to follow the motto of Professor Tsuchiya, which undoubtedly also applies well to our continuing fight against musculo-skeletal infections: "*Dream, dare, and do*" !

With warmest regards,

[**www.waiotcongress2024.com**]

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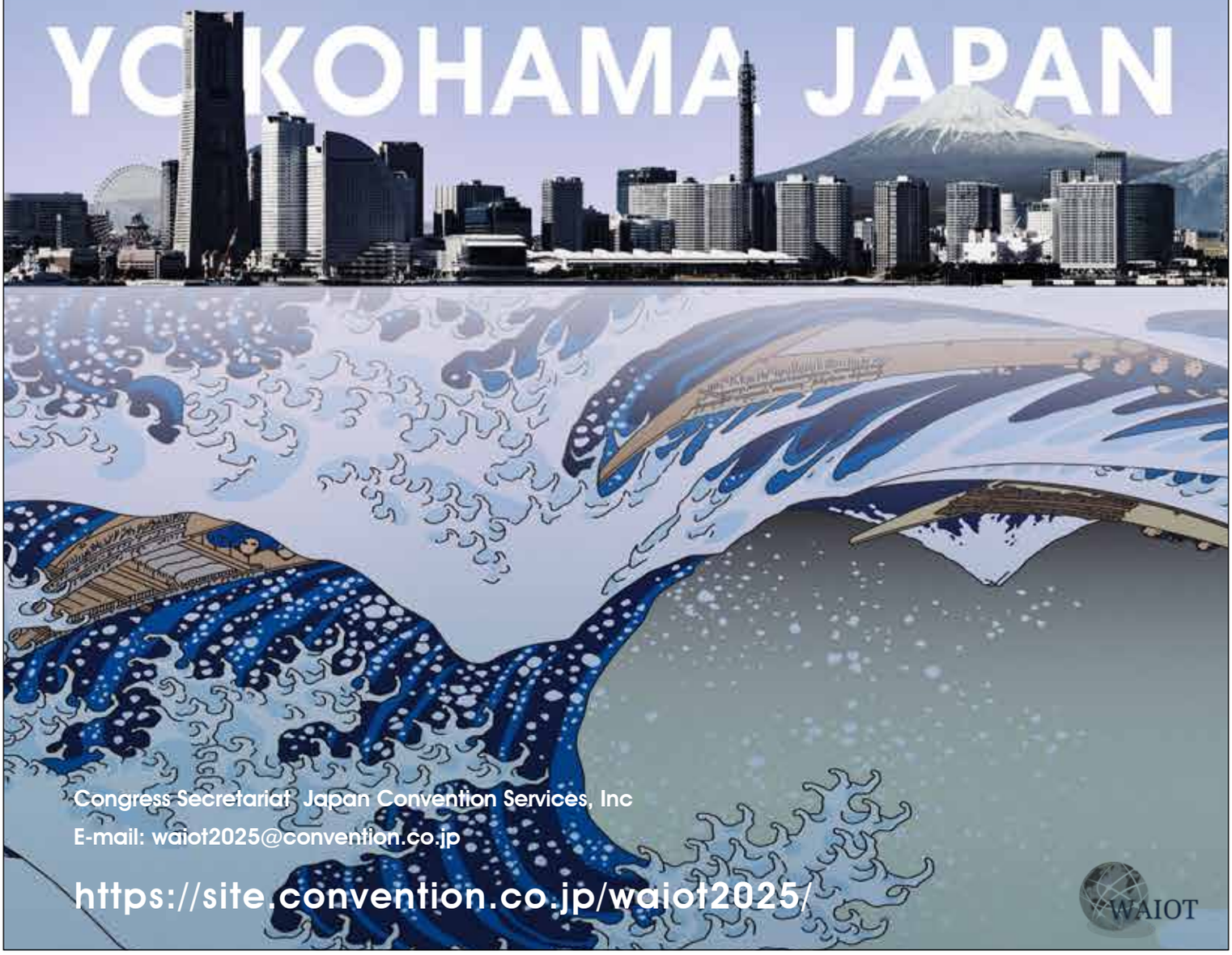

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WAIOT

: Why did you eventually choose orthopedic surgery?

H.T.: During my medical studies, I was exposed to various fields of medicine. However, I was particularly drawn to the orthopedic department. The atmosphere there was vibrant – patients, doctors, and nurses all seemed cheerful and energetic. Additionally, considering the aging population and the increasing number of elderly people, I recognized a growing need for orthopedic surgeons. I felt that orthopedics had great potential for growth and impact, which ultimately led me to choose this specialty.

: You mentioned robotic surgery earlier. What is your view on the current systems available? What benefits do they offer, and what do you think the next generation of surgical robots will bring?

H.T.: I am very excited about the robotic systems in orthopedic surgery, and I'm a strong believer in their potential. We have studied alignment and component placement extensively, and while there are already numerous studies out there, the precision achieved with robotics is extremely impressive. For the first time, surgeons are able to control every single step of the arthroplasty surgery with a very high precision.

: Did you stay at the same university for your orthopedic surgery training?

H.T.: : Yes, I remained at Kanazawa University. After graduating from medical school, I completed my residency at Kanazawa University Hospital. Subsequently, I entered the graduate school of medicine there to pursue my PhD. I thought that there is still room for basic research in orthopedics to be developed in Kanazawa.

: What was the topic of your PhD research?

H.T.: My PhD research focused on caffeine, specifically its effects on cancer cells. I discovered that caffeine inhibits DNA repair in cancer cells after they've been damaged. This was particularly relevant to my work in orthopedic oncology, as I was involved in sarcoma chemotherapy. My research led to the development of a new chemotherapy protocol for osteosarcoma and other sarcomas, which we called caffeine-potentiated chemotherapy. This approach significantly enhanced the effectiveness of anti-cancer drugs, allowing us to minimize tumor excision and preserve more healthy soft tissue, muscles, nerves, and blood vessels, ultimately leading to better limb function for patients in addition to improving survival rates.

: When did you complete your PhD?

H.T.: I graduated from medical school in 1983 and spent five years on my PhD studies at Graduate School of Medical Sciences, Kanazawa University. I received my PhD in 1988.

: Were you already interested in orthopedic tumor surgery at that time?

H.T.: Yes, I was already deeply interested in musculoskeletal oncology during my PhD studies and early career because musculoskeletal oncology is the most challenging area in Orthopedic surgery. It is necessary for musculoskeletal oncology to bring together all the knowledge and skills in the field of orthopedics.

: What came next in your career?

H.T.: After completing my PhD, I became fully immersed in musculoskeletal oncology, developing various surgical procedures. In the early 1990s, I encountered the Ilizarov method, which involves bone lengthening and distraction osteogenesis. This technique, using external fixation, proved valuable for fractures, limb lengthening, bone defect reconstruction, and treating osteomyelitis. I also tackled many challenging cases of infected non-union, which was a significant problem in orthopedic surgery. My work naturally led me to focus on orthopedic infections in both tumor surgery and Ilizarov procedures.

: Where were you working during this time?

H.T.: I remained at Kanazawa University Hospital throughout my career, from the beginning until my retirement. I maintained a very consistent path, staying with the same institution throughout my professional life.

: Did you complete any fellowships abroad or at other hospitals?

H.T.: Yes, I spent almost a year at the University of Vienna under the supervision of Professor Rainer Kotz, a renowned tumor surgeon who developed modular tumor prostheses. Vienna University was and still is famous for orthopedic surgery. This fellowship took place from 1991 to 1992. Additionally, I enjoyed several traveling fellowships to the United States, visiting five times to study tumor surgery and the Ilizarov method of external fixation.

: Who were some of the important mentors in the early part of your career?

H.T.: While I've had many influential figures in my career, including professors from my orthopedic department and international mentors like Professor Rainer Kotz, I want to emphasize that my most important mentors have been my patients. They've taught me invaluable lessons throughout my career. Of course, I also greatly respect my predecessors - all the great orthopedic surgeons who have achieved so much in our field. But primarily, I consider my patients to be my greatest teachers.

: Can you tell us about your work environment and how orthopedic departments are typically organized in Japan?

H.T.: I became a professor and chairman of the department in 2010. At that time, I had over 80 graduate students pursuing their PhDs under my supervision. I also taught numerous medical students. Our department consisted of about 15 staff members, including myself as professor and chairman, one professor, two associate professors, two lecturers, and several assistant professors. We were organized into specialized teams: tumor, spine, joint, hand, foot and ankle, sport medicine and rehabilitation. This structure allowed us to cover all fields of orthopedic surgery within the department, with a range of professionals in each area.

: Are there specific fields within orthopedics that particularly interest you?

H.T.: My main interests lie in musculoskeletal oncology and the Ilizarov method, which includes treating bone infections. I was also heavily involved in basic research. However, as the department head, I oversaw and managed all fields of orthopedic surgery.

: Regarding musculoskeletal tumor surgery and infection, have you seen advancements with implants, such as nanotechnology? What are your thoughts on this?

H.T.: Indeed, there have been significant advancements. In tumor surgery, the infection rate is quite high compared to other orthopedic surgeries - about 10 to 20 times higher. Recognizing this issue, I've been working on developing antimicrobial implants. Around 2006 or 2007, I developed an antibacterial coating for orthopedic implants using iodine. Iodine is a highly effective element for controlling infection. We've patented this technology, and I'm currently waiting for iodine-coated implants to enter the market. We expect a total hip system coated with iodine to become available by the end of this year or next year.

: Which company is working on this patented technology?

H.T.: While I was initially unsure if I could disclose this information, it's actually public knowledge. The company working on this is an American company.

: How are bone and joint infections typically managed in Japan? Is there a specific network or national society focused on this?

H.T.: Yes, we have the Japanese Society for Study of Bone and Joint Infections, which is a very well-established organization with a history of about 50 years. Additionally, I'm a member of the Japan Association for the Study of External Fixation and Limb Lengthening (ASAMI-Japan). The introduction of the Ilizarov method has significantly improved our ability to treat difficult cases of infected non-union and osteomyelitis.

: What are the main bacteria causing infections in Japan?

H.T.: The bacterial profile is similar to what you'd find worldwide. Staphylococcus aureus is the most common, with MRSA cases increasing. We also encounter mixed infections, including Staphylococcus epidermidis, Pseudomonas aeruginosa and so on. Fungal infections are particularly challenging to treat.

: What about antibiotic-resistant bacteria?

H.T.: We're seeing an increase in antibiotic-resistant bacteria, largely due to the widespread use of antibiotics. This is why I've been focusing on developing the iodine coating for implants. Iodine is effective against bacteria, viruses, and fungi without inducing resistance, making it an excellent material for infection control.

: Can you tell us more about the development of the iodine coating?

H.T.: I began developing the iodine coating around 2006-2007. It was a collaborative effort involving the microbiology department at our university, the orthopedic surgery department, and the Chiba Institute of Technology. Professor Takaya, an engineer from Chiba Institute who unfortunately passed away over 10 years ago, played a crucial role in developing the iodine treatment technology.

The coating can be applied to all titanium implants, which are widely used in orthopedics. This includes hip and knee implants, fracture fixation materials like intramedullary nails and locking plates, and spinal instrumentation. However, it's not possible to apply the coating to stainless steel or cobalt-chrome implants.

: Are there other innovations in the field of bone and joint infection (BJI) treatment in Japan, such as phage therapy?

H.T.: Phage therapy is not currently available in Japan. As for BJI treatment, we follow standard protocols. For early-stage infections, we attempt DAIR (Debridement, Antibiotics, Implant Retention). If that's not possible, we proceed with either one-stage or two-stage revision surgery. We use antibiotic-impregnated bone cement, typically with vancomycin or sometimes a combination of two antibiotics. The choice between one-stage and two-stage revision remains debatable, but in my practice, I generally prefer the two-stage approach, especially for more complex cases.

: How do you manage soft tissue issues? Do you collaborate with plastic surgeons for procedures like muscular flaps?

H.T.: In our department, we have our own microsurgical team capable of perform-

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ing various procedures, including flaps, vascularized bone transfers, and myocutaneous flaps. This in-house expertise is very useful for managing complex cases.

: Do you combine bone transfer techniques with the Ilizarov method?

H.T.: Yes, I'm particularly fond of the Ilizarov method, especially bone transport. It's an excellent procedure for controlling infection and addressing bone defects. As Ilizarov said, "In the fire of bone regeneration, infection will be burned out." However, it's crucial to have expertise in using this technique.

: Is the Ilizarov method widely known among orthopedic surgeons in Japan?

H.T.: Yes, it's relatively well-known in Japan. The ASAMI Japan Society, which focuses on the Ilizarov method and external fixation, has over 250 members. More than 200 orthopedic surgeons in Japan can perform correct Ilizarov procedures. I initially learned about external fixation and the Ilizarov method from American and Italian doctors, including Maurizio Catagni in Lecco, Italy. In the United States, I learned a lot from Dr. Paley and Dr. Herzenberg. I spent time as a traveling fellow at their institute before bringing these techniques back to Japan.

: How many patients have you treated using the Ilizarov method in Japan?

H.T.: I began using the Ilizarov method in 1992-1993, so it's been nearly 30 years now. Over this period, I've treated more than 1,000 patients using the Ilizarov procedure with external fixation, bone lengthening, and bone transport. I've even applied the Ilizarov method for reconstruction in tumor patients. In fact, I believe I was the first to use bone transport for reconstruction after tumor resection.

: Are there any societies in Japan or international societies that you find interesting and have been happy to be involved with?

H.T.: Certainly. The largest Japanese society I'm involved with is the Japanese Orthopaedic Association (JOA). It currently has about 26,000 members. I served as a board member for several years, and three years ago, I had the honor of being the congress president for the annual JOA meeting in Tokyo.

I'm also involved in other orthopedic societies, including those focused on pediatric orthopedics and tumor research. Internationally, I'm currently a board member of the World Association against Infection in Orthopaedics, Trauma (WAIOT) and the International Society of Limb Salvage (ISOLS) and Asian Pacific Musculoskeletal Tumor Society (APMSTS). I was previously a committee member of the SICOT Infection committee, but I've since stepped down from that role.

: Can you tell us a little bit about the International Society of Limb Salvage?

H.T.: The International Society of Limb Salvage (ISOLS) was established in 1981 by a group of tumor surgeons. Since then, limb salvage surgery in musculoskeletal oncology has become widely adopted and refined. Today, we can perform limb-sparing surgery very safely based on a strategy that combines adequate chemotherapy, precise tumor excision, and appropriate reconstruction. In advanced countries, the limb salvage rate for osteosarcoma is now probably over 90%.

About 85-90% of ISOLS members are orthopedic surgeons, with the remainder being chemotherapists, radiologists, pathologists, and occasionally radiotherapists. This multidisciplinary approach is crucial in the field of musculoskeletal oncology.

In 2017, I had the privilege of hosting the ISOLS meeting in my city, Kanazawa, as the congress president. Following that, I served as the society's president from 2017 to 2019.

During my career, I've developed several innovative procedures. One that I'm particularly proud of is the frozen autograft technique. This involves freezing the resected tumor bone in liquid nitrogen for 20 minutes, which effectively kills all cells while preserving the bone structure. The treated bone can then be reimplanted, and over time, it becomes revitalized as osteogenic cells and blood vessels grow into it. This procedure has now been adopted worldwide, including in several European countries.I've also developed other techniques, such as iodine coating for antibacterial implants and a caffeine-potentiated chemotherapy method. Unfortunately, we didn't secure a patent for the latter, so it hasn't been commercialized.

: Can you tell us about your work on osteomyelitis and chronic infected non-union?

H.T.: : I've developed an interesting procedure for treating osteomyelitis and chronic infected non-union. After thoroughly debriding the infected area, we irrigate it with an iodine solution. Then, we reconstruct the bony defect or cavity using a paste-like bone substitute, typically α-Tricalcium phosphate (αTCP), mixed with antibiotics.

This method is superior to using antibiotic-loaded bone cement because it allows for a much higher release of antibiotics over time. With bone cement, less than 10% of the antibiotics are typically released, whereas with this bone substitute method, more than 80% of the antibiotics are released over a period of 3-4 weeks. This makes it very effective in controlling infection.

We can use various antibiotics with this method, including vancomycin. It's particularly effective for infected non-union cases where we can preserve one cortical wall and apply the antibiotic-loaded bone substitute. Over time, this leads to union and control of the infection.

: You are doing basic research too, any work you'd like to mention?

H.T.: Yes, I'd like to mention my work in regenerative medicine using stem cells. I'm particularly interested in using fat-derived stem cells for bone regeneration and union. These cells are also very effective against infection because they produce antibacterial peptides. We've found that combining fat-derived stem cells with antibiotics creates a synergistic effect, especially useful in treating septic arthritis. We've already published on this topic.

: Can you give us some historical perspective on WAIOT and why you've been interested in being involved?

H.T.: My involvement with WAIOT (World Association against Infection in Orthopedics and Trauma) began about seven or eight years ago when I met Carlo Romano at a Greek Orthopaedic Association meeting organized by Professor Konstantinos Malizos. I presented on iodine coating, and Carlo discussed his work on antibiotic gel. We became good friends, and Carlo introduced me to WAIOT, encouraging me to join. Since then, I've been actively

involved with WAIOT. I organized the annual meeting of the Japan Bone and Joint Infection Society in Kanazawa, where I invited both Carlo and Dr. Javad Parvizi, an authority on periprosthetic joint infection (PJI).

This year, the WAIOT meeting is being organized by Dr. Joseph Benevenia in the United States. Following that, I'll have the honour of being the president of WAIOT and organizing the WAIOT meeting in Yokohama, Japan, in September 2025 together with the Congress President Professor Yutaka Inaba, Professor and Chairman, Department of Orthopaedics, Yokohama City University.

: What would you like to focus on during the WAIOT conference in Japan?

H.T.: For the upcoming WAIOT meeting in Japan, we plan to cover a wide range of orthopedic fields, including spine, hand, foot, and trauma. Given my co-worker's expertise, one symposium will certainly focus on periprosthetic joint infection (PJI), covering its prevention, diagnosis, and treatment.Personally, I'm very interested in antibacterial materials and coatings, including the use of iodine, antibiotics, and potentially silver. We'll also discuss innovative approaches like Carlo's antibiotic gel.

Our goal is to make the WAIOT meeting in Japan very fruitful, combining cutting-edge scientific discussions with engaging social events.

: As a final question, what advice would you give to young surgeons who look up to your career and achievements?

H.T.: : My advice to young doctors can be summed up in a few key points. First, my motto: "*Dream, dare, and do*." It's about challenging yourself and realizing your dreams.

Second, I always tell young doctors in our department to "*be cheerful, be joyful, and be energetic*." This positive attitude is crucial for success in your dreams.

Lastly, I'd like to share a quote from the father of rocketry, which has always inspired me: "*It is difficult to say what is impossible, for the dream of yesterday is the hope of today and the reality of tomorrow.*" This encapsulates my belief in the power of perseverance and innovation. ■

MULTI-DRUG RESISTANT BACTERIA AND THE ROLE OF BACTERIAL BIOFILMS IN WAR-RELATED MUSCULOSKELETAL INFECTIONS: A NARRATIVE REVIEW.

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INTRODUCTION

In the crucible of conflict, where the chaos of battle unfolds, the toll on human life and limb extends far beyond the immediate violence of warfare. Amidst the debris of shattered landscapes and fractured societies, another silent adversary lurks, imperiling the lives of those wounded in combat: multi-drug resistant bacteria (MDR).

The convergence of traumatic injuries, compromised healthcare infrastructure, and the indiscriminate use of antimicrobial agents has catalyzed the emergence of MDR pathogens, posing a grave threat to military personnel and civilian populations alike. Nowhere is this threat more acutely felt than in the domain of war-related musculoskeletal infections, where the intricate interplay between microbial colonization, host immune responses, and environmental factors shapes the trajectory of disease.

To appreciate the magnitude of this challenge, one must first understand the formidable arsenal of resistance mechanisms deployed by MDR bacteria. The advent of antibiotics heralded a golden age of modern medicine, offering a panacea for infectious diseases that had long plagued humanity. However, the indiscriminate use and misuse of these agents have fueled the evolution of resistance among pathogenic bacteria, rendering once-potent antibiotics impotent against their targets. The genetic plasticity of bacteria, coupled with the selective pressure exerted by antimicrobial agents, has engendered a relentless arms race between the forces of medicine and microbial adaptation. [1]

In the theatre of war, where the exigencies of combat demand rapid and decisive action, the consequences of antimicrobial resistance are particularly dire. Traumatic injuries sustained in battle often involve extensive soft tissue damage, open fractures, and foreign body contamination, creating an ideal milieu for bacterial colonization and subsequent infection. Moreover, the chaotic nature of warfare may impede access to timely medical care, leading to delays in wound management and increasing the risk of infection. [2] This is also facilitated by the fact that military personnel are always in stressful situations, often experiencing hunger and thirst. Their sanitary condition, especially soiled clothing, leaves much to be desired.

In every army around the world, strict rules exist for providing assistance to the wounded, including a system for evacuating the wounded from the battlefield to medical facilities. Staged evacuation of the injured is the process of transporting wounded individuals from the site of injury to larger or specialized medical facilities to provide them with appropriate medical care. During staged evacuation, patients go through several stages of assistance and transportation, starting from primary medical care on the battlefield and ending with hospitalization in specialized hospitals or clinics. At each stage of evacuation, in addition to providing medical care to the patient, broad-spectrum antibiotics can be administered inadequately.

Compounding these challenges is the insidious nature of bacterial biofilms, complex microbial communities encased within a self-produced extracellular matrix. Biofilms exhibit a remarkable resilience to antimicrobial agents and host immune defenses, rendering traditional treatment modalities ineffective against chronic and recurrent infections. Within the context of war-related musculoskeletal injuries, biofilms serve as clandestine sanctuaries for MDR pathogens, perpetuating the cycle of infection and thwarting attempts at eradication. [3] The particular danger of these biofilms lies in their ability to colonize large bone fragments and pieces of necrotic tissue resulting from high-energy trauma caused by bullets and shrapnel.

To address the growing threat of MDR bacteria and bacterial biofilms in war-related musculoskeletal infections, a multidisciplinary approach is imperative. Clinicians, microbiologists, epidemiologists, and policymakers must collaborate to develop innovative strategies for prevention, diagnosis, and treatment.

This narrative review aims to synthesize the existing literature on this topic, shedding light on the relevance of antimicrobial resistance and the role biofilm formation in the context of combat-related injuries.

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METHODS

Full-text papers and those with an abstract in English published from 2004 to December 2023, identified through international databases, were investigated with the following keywords variably pooled: "*Multidrug-resistant bacteria in battlefield wounds*", "*Antibiotic resistance in combat zones*", "*MDR*", "*Antibiotic resistance*" "*Bacteria*", *Infection*", "*Osteomyelitis*", "*War*", "*Battlefield*", "*Wound*", "*Biofilm*".

Those reporting the incidence of MDR bacteria in battlefield wounds were included as well as those papers investigating the role of bacterial biofilms in war-related MSIs. Organisms were classified as MDR if they were resistant to 3 or more classes of antibiotic agents (aminoglycosides, betalactams, carbapenems, and fluoroquinolones) or if they expressed extended-spectrum b-lactamases or carbapenemases. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci were also considered MDR.

Data were pooled for further analysis in order to answer the following questions:

1. What is the impact of conflicts on the mortality rate in the world today ?
2. What is the incidence of war-related musculo-skeletal infections (W-MSIs)?
3. What is the role, if any, of bacterial biofilms in W-MSIs ?
4. What are the main drivers that sustain the occurrence of MDR bacteria in W-MSIs and which preventive measures can be effectively be applied?

The impact of conflicts on the mortality rate in the world today

The number of armed conflicts globally peaked a record high with 182 wars and minor conflicts recorded in 2017, according to the Uppsala Conflict Data Program (UCDP) (cf. **https://www.uu.se/en/department/peace-and-conflict-research/research/ucdp/**). As of our last update in June 2024, several ongoing conflicts and areas of instability persist around the world. Here are some of the main ones:

1. **Syrian Civil War**: The conflict in Syria has been ongoing since 2011, with various factions, including the Syrian government, rebel groups, Kurdish forces, and extremist organizations, vying for control. The war has resulted in significant humanitarian suffering and displacement.

2. **Yemeni Civil War**: Yemen has been engulfed in a civil war since 2014, with Houthi rebels fighting against the internationally recognized government supported by a coalition led by Saudi Arabia and the United Arab Emirates. The conflict has led to a dire humanitarian crisis, including widespread famine and disease outbreaks.

3. **Conflict in Afghanistan**: While the United States officially withdrew its troops from Afghanistan in 2021, the country remains embroiled in conflict. The Taliban has regained control of much of the country, leading to concern about human rights abuses.

4. **India-Pakistan conflict**: the confrontation arose out of the 1947 Partition of British India, enshrined in the Indian Independence Act. The Partition established a Muslim-majority Pakistan and a Hindu-majority India and provided the diverse regions of Jammu and Kashmir the opportunity to choose which country to accede to. The maharaja (Kashmir's monarch) ultimately agreed to join India in exchange for help against invading Pakistani herders, triggering the Indo-Pakistani War of 1947-48 and subsequent conflicts. Violence along the India-Pakistan border never completely subsided and continues with incidents reciprocal accusations.

5. **Tigray Conflict (Ethiopia)**: Since November 2020, Ethiopia's Tigray region has been the site of a conflict between Ethiopian federal forces and the Tigray People's Liberation Front (TPLF). The conflict has led to widespread displacement, reports of atrocities, and a humanitarian crisis.

6. **Conflict in the Sahel Region**: Countries in the Sahel region of Africa, including Mali, Burkina Faso, Niger, and Chad, are facing ongoing instability due to the presence of jihadist groups, ethnic tensions, and governance challenges. Military interventions and peacekeeping efforts are ongoing to address the crisis.

7. **Nagorno-Karabakh Conflict**: The conflict between Armenia and Azerbaijan over the disputed region of Nagorno-Karabakh flared up in 2020, leading to a brief but intense war. A ceasefire brokered by Russia has been in place, but tensions remain high, and sporadic clashes continue.

8. **Conflict in Libya**: Libya has been mired in conflict since the overthrow of Muammar Gaddafi in 2011, with various armed groups vying for power and control. Efforts to broker a lasting ceasefire and political reconciliation are ongoing

9. **Conflict in Eastern Ukraine**: Since 2014, Ukraine has been locked in a conflict with Russian-backed separatists in the eastern regions of Donetsk and Luhansk. Despite ceasefire agreements, a major conflict emerged as of February 2022, leading to a direct confrontation between Russia and Ukraine, supported by several western Countries, leading to hundreds of thousands of casualties and displacement.

10. **Israeli-Palestinian conflict** dates back to the end of nineteenth century. As the most recent development of this ongoing conflict, Hamas launched a deadly attack on Israel on October 7, 2023, prompting the Israel government to engage in aerial campaigns and ground operations within the Gaza Strip. As a result, almost two million Gazans—more than 85 percent of the population—have fled their homes since October 2023. Recent casualty estimates from the Hamas-run Gazan Health Ministry place the death and wounded toll in Gaza to tens of thousands, with a raise of tensions among countries in the Middle-East and beyond.

These are just a few examples of several ongoing conflicts around the world, and the situation in each region is complex and dynamic, with various factors contributing to instability and violence (Figure 1).

Death toll related to armed conflicts varies across continents from 19 to 307 per 100.000 habitants (Figure 2). Excluding battle-related deaths, wars have been found to be associated with an increase in age-standardized all-cause mortality of 81.5 per 100,000 population.

Figure 1: Major ongoing conflicts and instability areas in the world as of June 2024
(source: https://www.cfr.org/global-conflict-tracker)

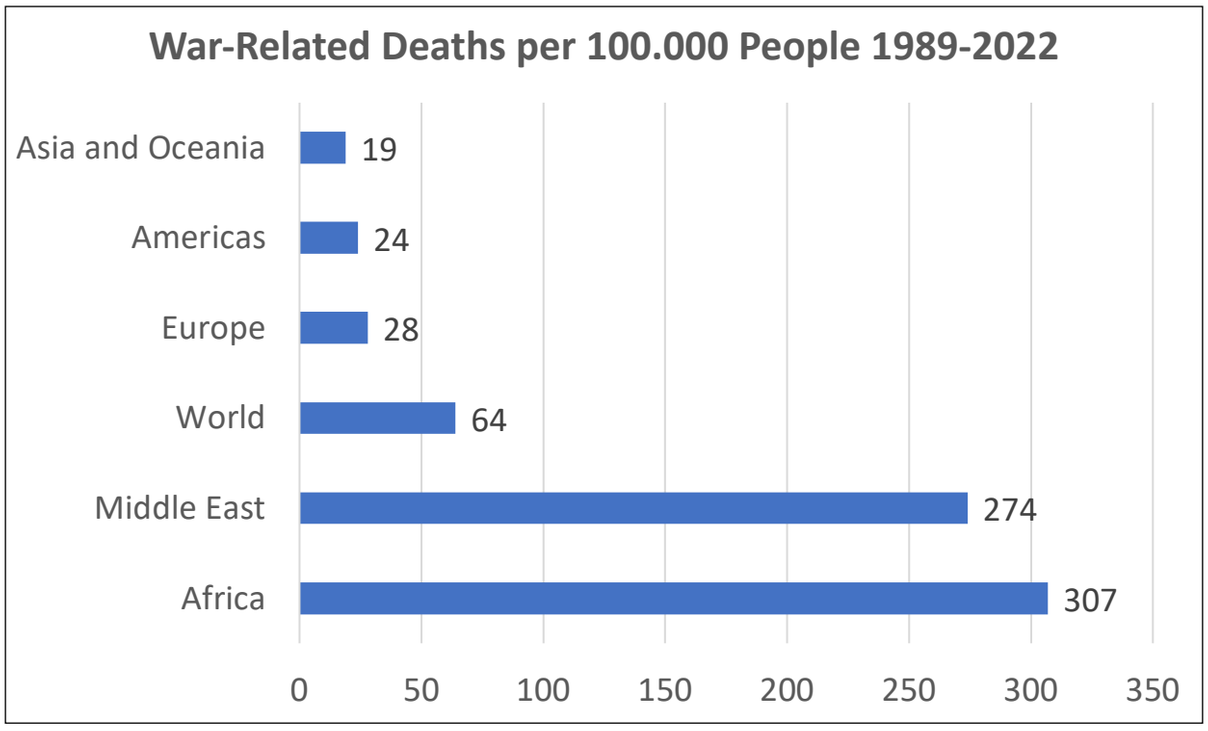

Figure 2: . Death rates in armed conflicts based on the continent they occurred, 1989-2022. Deaths of combatants and civilians due to fighting, per 100,000 people of the population in 1989. Included are all armed conflicts that were ongoing over that time.
(source: Uppsala Conflict Data Program (2023); Natural Earth (2022) – processed by Our World in Data; https://ourworldindata.org/war-and-peace#all-charts)

For comparison, according to the World Health Organization [4] the 10 leading medical causes of death, globally, in 2016 showed the following crude death rate, per 100,000 population:

1. Ischaemic heart disease, 126
2. Stroke, 77
3. Chronic obstructive pulmonary disease, 41
4. Lower respiratory infections, 40
5. Alzheimer's disease and other dementias, 27
6. Trachea, bronchus, and lung cancers, 23
7. Diabetes mellitus, 21
8. Road injury, 19
9. Diarrhoeal diseases, 19
10. Tuberculosis, 17

Incidence of MDR bacteria in War-related MSIs

Author	Year of publication	Battlefield theatre(s)	Number of patients
Murray et al. [6]	2009	Iraq and Afghanistan	2242
Weintrob et al. [7]	2018	Iraq and Afghanistan	1807
Tribble et al. [8]	2019	Iraq and Afghanistan	1359
Fily et al. [9]	2019	Iraq, Yemen and Syria	727
Kiley et al. [10]	2021	Iraq and Afghanistan	51
Yaacoub et al. [11]	2022	Syria, Iraq, Lebanon, Palestine, and Yemen	3204
M'Aider et. [12]	2022	Iraq	174
Soderstrom et al. [13]	2023	Afghanistan	316
Moussally et al. [14]	2023	Gaza	n/a

Table 1. Papers reporting the incidence of MDR in W-MSIs.

Obtaining precise incidence and prevalence data specifically for MDR bacteria in W-MSIs is challenging, due to the variability of conflict settings, healthcare infrastructure, and reporting mechanisms. [5]

In fact, the most common pathogens found in war-related musculoskeletal infections can vary depending on factors such as the geographic location of conflict, the nature of injuries sustained, and the healthcare resources available for treatment. However, a number of studies have identified certain pathogens that are frequently implicated in these infections.

Nine original articles reporting the incidence of MDR bacteria in W-MSIs and one study dealing with the impact of bacterial biofilms in war-related injuries we included in our analysis (cf. Table 1).

Data were collected by the following battlefield theatres: Iraq, Syria, Lebanon, Palestine, Yemen, Afghanistan. Analysis of the available studies revealed that the majority come from few groups of researchers, with an absolute prevalence of papers published from US and German military centres.

According to our search, both Gram positive and negative MDR bacteria are frequently associated with W-MSIs in various battlefield theatres.

Some of the most common pathogens found in war-related musculoskeletal infections include:

1. Acinetobacter baumannii: This gram-negative bacterium is notorious for its ability to survive in hospital environments and cause nosocomial infections. It has been frequently isolated from wounds of military personnel injured in combat, particularly in regions such as Iraq and Afghanistan.

2. Pseudomonas aeruginosa: Another gram-negative bacterium, Pseudomonas aeruginosa, is commonly associated with war-related musculoskeletal infections. It is known for its intrinsic resistance to many antibiotics and its ability to form biofilms, making treatment challenging and requiring extensive infected bone removal.

3. Escherichia coli: While often associated with urinary tract infections, Escherichia coli can also cause musculoskeletal infections, particularly in the context of penetrating wounds or open fractures sustained in combat. Some strains of E. coli may exhibit multidrug resistance, further complicating treatment.

4. Klebsiella pneumoniae: Like E. coli, Klebsiella pneumoniae is a gram-negative bacterium that can cause a range of infections, including musculoskeletal infections in the setting of trauma. Multidrug-resistant strains of K. pneumoniae have been identified in combat-related wounds, posing challenges for treatment.

5. Staphylococcus aureus: This gram-positive bacterium is a common cause of both community-acquired and nosocomial infections. Methicillin-resistant Staphylococcus aureus (MRSA) has garnered particular attention due to its resistance to multiple antibiotics and its ability to cause severe infections in wounded combatants.

6. Enterococcus species: Enterococci, particularly Enterococcus faecalis and Enterococcus faecium, are gram-positive bacteria that can cause infections in wounds, especially in the context of healthcare-associated infections or in patients with compromised immune systems. Enterococcal infections may be challenging to treat due to intrinsic and acquired resistance to antibiotics.

These pathogens represent some of the most common causes of musculoskeletal infections in military personnel injured in combat. However, the microbiological profile of these infections may vary depending on factors such as the specific circumstances of the conflict, the availability of medical resources, and local antimicrobial resistance patterns.

In fact, obtaining precise incidence and prevalence data specifically for multi-drug resistant bacteria (MDR) in war-related musculoskeletal infections can be challenging due to the variabili-

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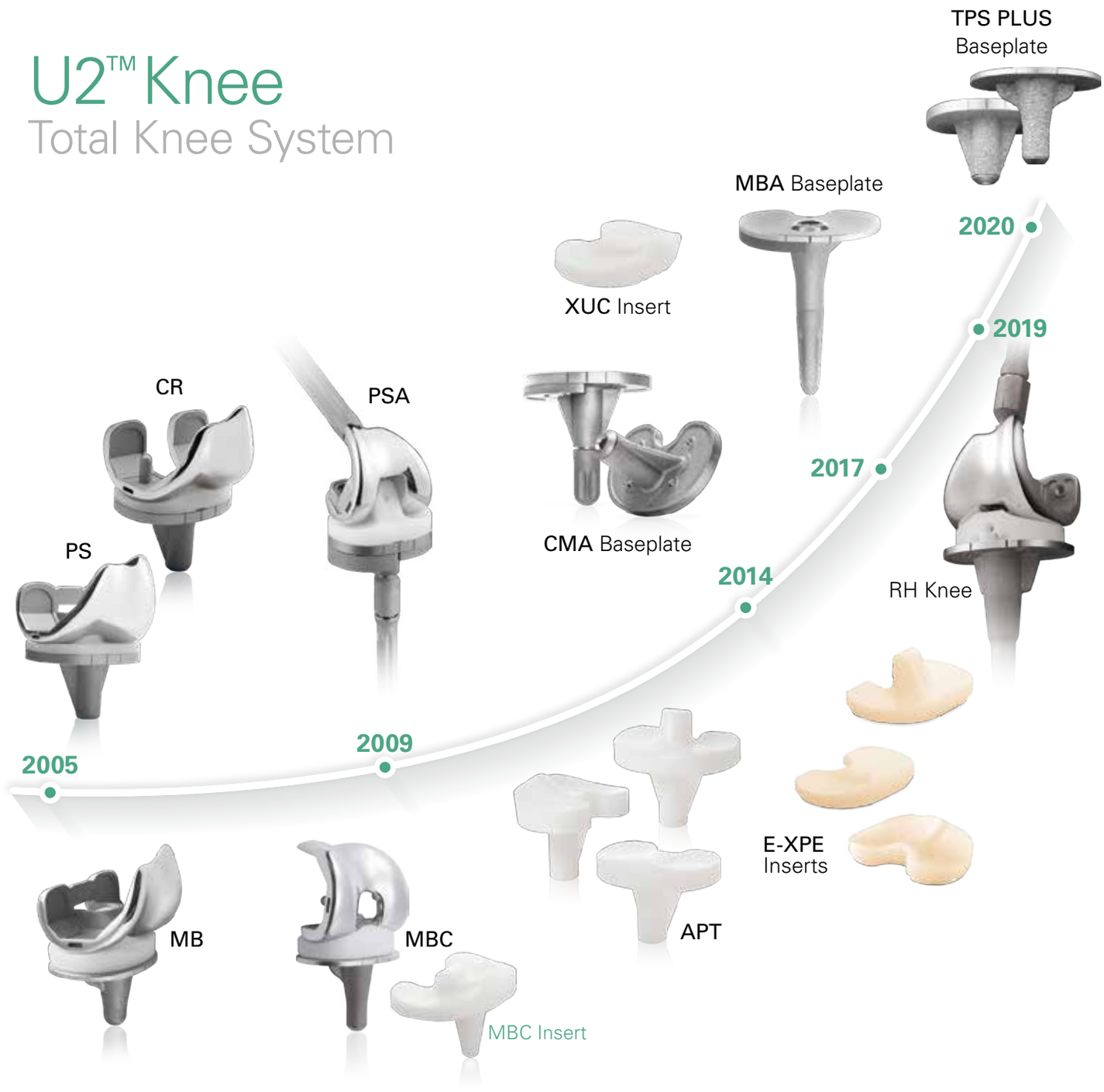

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ty of conflict settings, healthcare infrastructure, and reporting mechanisms.

According to the data available for our review, the reported incidence of MDR bacteria in W-MSIs was as high as 81% in patients with osteomyelitis, with up to 33% extended-spectrum beta-lactamases found in Gram-negative isolates, and almost 25% Enterobacteriaceae being resistant to carbapenem. In particular, MDR found in skin and soft tissues and bones included Staph. aureus (range 21.3% to 60.5%), Enterobacteriaceae (12.5% to 86.2%), P. aeruginosa (7.6% to 53.4%), Enterococci species (3.2% to 74.0%), A. baumannii (45% to 86.2%). Escherichia coli (78.3%), Klebsiella spp. (45%); Coagulase negative Staphylococcus and Anaerobes showed much lower or null MDR isolates (cf. Table 2).

Microorganism	% of positive isolates	Rate of MDR strains
Staphylococcus aureus	23.2 to 49.1%	21.3 to 60.5%
Coagulase negative Staphylococcus	5.7%	0%
Anaerobes	12.5%	0%
Klebsiella spp.	25%	45%
Pseudomonas aeruginosa	10.3 to 13.5%	7.6 to 53.4%
Enterobacteriaceae	6.1 to 31.5%	25%
Escherichia coli	8.8%	78.3%
Acinetobacter baumannii	2 to 11.0%	45 to 86.2%
Enterococci spp.	3.2 to 8.0%	3.2 to 74%

Table 2. Most frequently isolated pathogens from bone and skin and soft tissue injuries with the relative range of MDR strains, according to the authors reported in Table 1.

The role of bacterial biofilms in W-MSIs

Biofilm formation was significantly associated with infection persistence in a univariate analysis performed in the only study that we could found on this topic. [15] In their research, Akers and co-workers tested for biofilm formation in a total of 235 bacterial isolates from military personnel with deployment-related injuries in a case-control analysis. The authors concluded that, although limited by the relatively small sample size, their study confirmed that biofilm production by clinical strains is significantly associated with the persistence of wound infections.

Various mechanisms may sustain bacterial biofilms formation in war-related bone and joint infections, including:

1. Prolonged Wound Healing: In the chaotic and resource-limited environments of conflict zones, prompt and effective wound management may be difficult to achieve. Traumatic injuries sustained in warfare often involve open comminuted fractures, penetrating wounds, and tissue damage, creating ideal conditions for bacterial colonization and biofilm formation. Bacterial biofilms delay wound healing processes, prolonging the recovery time for injured military personnel and increasing the risk of complications.

2. Foreign Body and Implant-Associated Infections: War-related injuries are frequently associated with retained contaminated foreign body and often necessitate the implantation of orthopedic hardware or prosthetic joints to stabilize fractures or replace damaged tissues. All these materials can serve as substrates for bacterial adherence and biofilm formation.

3. Antimicrobial Resistance: Bacterial biofilms provide a protective niche for MDR pathogens, shielding them from the lethal effects of antibiotics and offering an additional possibility to exchange antibiotic resistance genetic information.

4. Chronicity and Recurrence: The resilience of biofilm-associated bacteria to host immune responses and antimicrobial agents allows infections to persist despite aggressive treatment measures.

5. Diagnostic Limitations: Diagnosing biofilm-associated infections in war-related bone and joint injuries presents significant challenges. Conventional diagnostic methods, such as tissue cultures or imaging studies, may fail to detect biofilm-embedded bacteria, leading to delayed or inaccurate diagnosis. Improved diagnostic techniques, such as antibiofilm pretreatment methods [16] are needed to enhance the accuracy of diagnosis and facilitate targeted treatment.

In summary, bacterial biofilms play a critical, although still underestimated and insufficiently studied, role in exacerbating the challenges associated with treating war-related bone and joint infections. Their ability to promote chronicity, antimicrobial resistance, and treatment failure underscores the importance of developing novel therapeutic strategies tailored to combat biofilm-associated infections in conflict settings.

What are the main drivers that sustain the occurrence of MDR bacteria in W-MSIs and which preventive measures can effectively be applied ?

The main drivers causing the high rate of MDR bacteria in W-MSIs and their relative impact are not completely understood.

Most often reported general explanations, more based on the knowledge deriving from the civil context than from proven evidence in battlefields, include:

1. High Exposure to Bacteria: In battlefield situations, soldiers are exposed to various environments where bacteria thrive, including soil, water, and contaminated surfaces. This increased exposure can lead to higher rates of bacterial colonization and infection.

2. Widespread Antibiotic Use: In combat zones, antibiotics are frequently used to treat injuries and prevent infections. However, misuse or overuse of antibiotics can promote the development of anti-

biotic-resistant bacteria. Soldiers may receive antibiotics prophylactically or for treatment, which can contribute to the selection of resistant strains.

3. Limited Medical Facilities and Resources: In some combat situations, medical resources may be limited, leading to challenges in wound care and infection control. Improper wound management, unavailability or delayed medical assistance can increase the risk of infection and the spread of MDR bacteria.

4. Complex Wound Types: Battlefield injuries can range from minor cuts and scrapes to severe trauma, such as gunshot wounds or blast injuries. These complex wounds create environments conducive to bacterial growth and can be difficult to treat effectively, especially if MDR bacteria are present.

5. Movement of Troops: Troops in combat zones often move frequently, which can make it challenging to ensure continuity of care and follow-up for wound management. This movement may also result in exposure to different bacterial strains and environments, further increasing the risk of MDR infections.

On the other hand, better scientifically grounded and more specific risk factors are reported in Table 3.

Interestingly, a number of other potential risk factors were disproven. In particular, more easily modifiable factors such as early operative intervention, combined antibiotic administration [7] and single-dose broad-spectrum antimicrobials at the point-of-injury [20] did not affect infection or colonization rates, confirming neither benefit nor harm. In line with these results, combined antibiotic prophylaxis cefazolin plus fluoroquinolones and/or aminoglycosides was not proven superior to cefazolin or clindamycin alone to prevent infection in extremity fractures in the studies reported by Tribble et al. [21] and by Lloyd and co-workers. [22]

Even the value of local application of local antibiotics, like vancomycin powder, although advocated by some authors does not seem to have sufficient scientific evidence support. [23]

In this context, generic measures are proposed to limit the occurrence of MDR pathogens and bone and joint infections in a battlefield. These include

Author	Year of publication	Number of patients	Main identified risk factor(s)
Murray et al. [17]	2011	405	Higher military Injury Severity Score
Weintrob et al. [7]	2018	1807	Amputations, blood transfusions, Injury Severity Score.
Petfield et al. [18]	2022	1271	Open fracture ≥IIIb, blast injuries, foreign body at fracture site (with/without orthopedic implant), moderate/severe muscle damage and/or necrosis, moderate/severe skin/soft-tissue damage
Fayad et al. [19]	2023	n/a	Inappropriate microbial therapies, limited resources, high heavy metal contamination in humans and the environment, lack of access to proper water, sanitation and hygiene (WASH)

Table 3. Main risk factors for W-MSIs reported by various authors.

1. Infection Control Measures:

- Implement strict infection control protocols, including hand hygiene, wound care, and environmental sanitation, to prevent the transmission of pathogens among wounded individuals and healthcare personnel.
- Use personal protective equipment (PPE), such as gloves and masks, to reduce the risk of cross-contamination and nosocomial infections in field hospitals and medical facilities.

2. Prompt Wound Management:

- Prioritize prompt and effective wound management to minimize the risk of infection following traumatic injuries sustained in combat. This includes thorough wound debridement, temporary immobilization, irrigation with antimicrobial solutions, and appropriate wound dressing to prevent bacterial colonization and biofilm formation.
- Utilize advanced wound care technologies, such as negative pressure wound therapy (NPWT) or antimicrobial dressings, to promote wound healing and reduce the risk of infection.

3. Early Detection and Diagnosis:

- Develop rapid diagnostic tests capable of detecting MDR pathogens and biofilm-associated infections in battlefield settings. Point-of-care testing devices that provide real-time results can facilitate timely initiation of targeted antimicrobial therapy and infection control measures. [24]
- Incorporate imaging modalities, such as ultrasound or portable X-ray machines, into field medical units to aid in the diagnosis of bone and joint infections and guide treatment decisions in specialized hospitals.

4. Antimicrobial Stewardship:

- Implement antimicrobial stewardship programs to optimize the use of antibiotics and minimize the development of antimicrobial resistance among bacterial pathogens. This includes judicious antibiotic prescribing, dose optimization, and de-escalation of therapy based on culture and susceptibility results.
- Utilize combination therapy or alternative antimicrobial agents when treating suspected or confirmed MDR infections to improve treatment efficacy and reduce the risk of treatment failure.

5. Surgical Intervention:

- Prioritizing surgical intervention, such as thorough debridement, meticulous removal of all non-soft tissue-bound bone fragments, extensive irrigation of wounds with antiseptics, and fracture fixation. Pro-

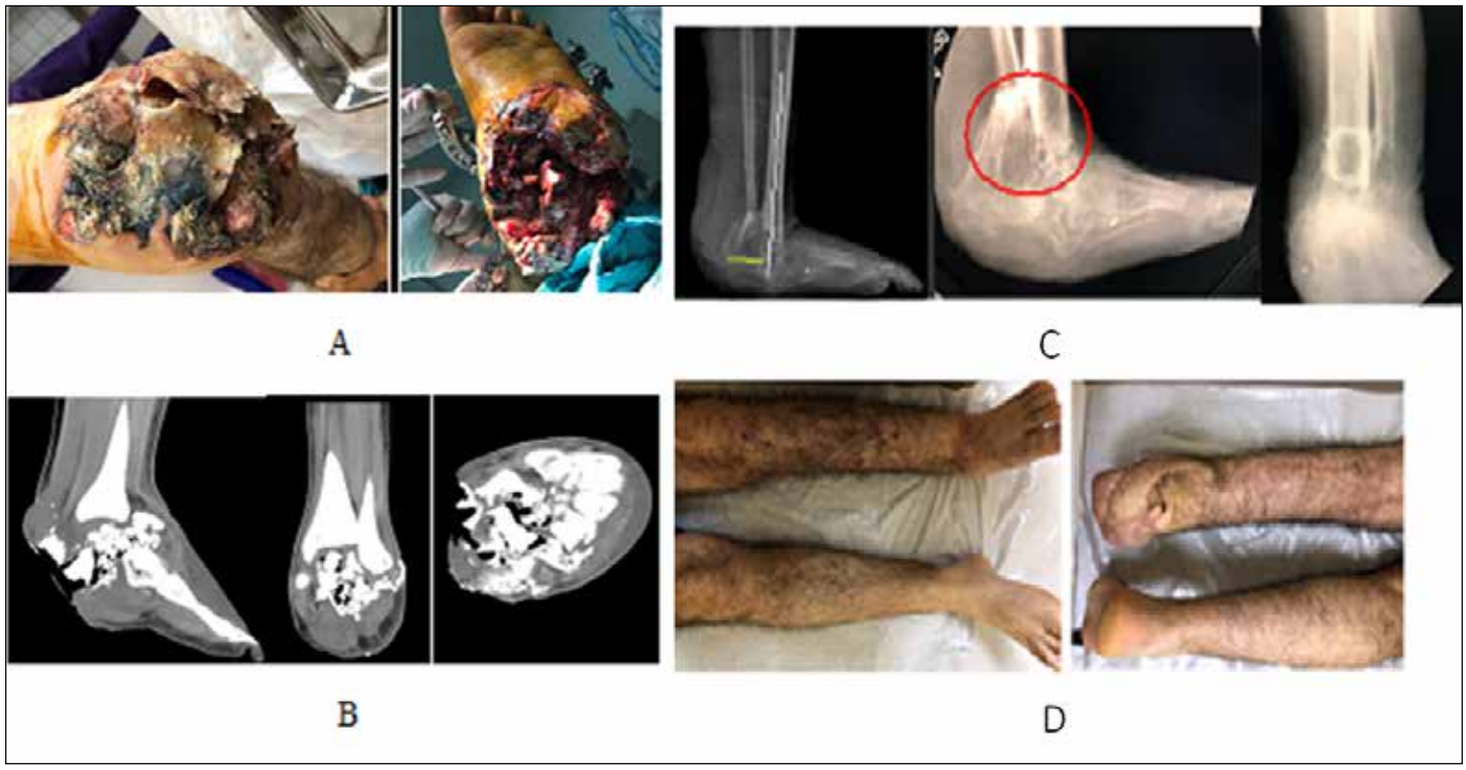

Figure 3: Patient M, 21 years old. A. Mine blast injury, soft tissue defects of right foot, extensive necrotic wound in the area of the left heel, comminuted fractures of the left calcaneus, talus, navicularis and cuboid bones. Admitted one month after the injury. Appearance of the wound at admission. B. CT scan of the foot at admission: comminuted fractures of the calcaneus, talus, navicularis and cuboid bones are visible. C. X-rays of the foot and ankle joint after completing treatment - 6 reconstructive surgeries (including 2 limb-lengthening by 4 cm each time). D. Clinical aspect at the end of treatments. [courtesy Prof. C. Alizadeh]

motion of wound healing in cases of traumatic injuries with suspected or confirmed bone and joint involvement. Utilization of various reconstructive surgery methods for wound closure when necessary (Figure 3).

- Consider early surgical consultation and intervention for cases of implant-associated infections or complicated fractures to prevent the establishment of biofilm-associated infections and reduce the risk of treatment failure.

6. Education and Training:

- Provide comprehensive education and training to military personnel, healthcare providers, and support staff on infection prevention practices, antimicrobial stewardship principles, and the recognition and management of bone and joint infections in battlefield settings.

- Foster a culture of awareness and accountability regarding the risks associated with MDR pathogens and the importance of adherence to infection control protocols and treatment guidelines.

By implementing a multidisciplinary approach that integrates infection control measures, early detection and diagnosis, antimicrobial stewardship, surgical intervention, and education, it is possible to limit the prevalence of MDR pathogens and bone and joint infections in a battlefield setting. Collaboration among military medical personnel, public health agencies, and research institutions is essential for developing and implementing effective strategies to mitigate the impact of infectious diseases in conflict zones.

CONCLUSIONS

In spite of the technological progress in all human fields and unprecedented direct communication means currently available between people and individuals, armed conflicts are still a widespread plague throughout the world and even increasing in number and intensity.In this context, the escalation of antimicrobial resistance threatens to undermine decades of medical progress, posing a significant risk to both civilian and military populations.

Nowhere is this threat more acutely felt than in the realm of war-related musculoskeletal infections, where the intersection of trauma, microbial colonization, and environmental factors creates a fertile breeding ground for resistance.

This narrative review provides further evidence of the extent and the severity of MDR bacteria in musculoskeletal infections and points out the need for further studies and large scale solutions. While several risk factors of W-MSIs have been identified, the majority of them appear unmodifiable; on the other hand, there is a lack of studies specifically addressing the etiopathogenesis of MDR infections after battlefield injuries. In fact, the most commonly reported genesis of MDR bacteria is the selective pressures exerted by the indiscriminate use of antibiotics, both on the battlefield and in civilian healthcare settings, even if a scientific demonstration of this assumption in battlefield injuries has never been produced and other mechanisms, like for example the cross-resistance to heavy metals and antibiotics are still insufficiently understood.

The evolution of resistance mechanisms, facilitated by genetic mutations and horizontal gene transfer, has endowed pathogens with an alarming repertoire of strategies to evade the lethal effects of antimicrobial agents. Compounding this challenge is the ability of bacteria to modulate their physiological state within biofilms, exhibiting altered metabolic activity and gene expression profiles that confer enhanced resistance to antibiotics. Consequently, the efficacy of traditional treatment regimens is severely compromised, necessitating a paradigm shift in therapeutic approaches towards more targeted and multifaceted interventions.

In war-related musculoskeletal infections, the clinical implications of MDR bacteria and biofilm-mediated resistance are profound. Traumatic injuries sustained in combat frequently involve extensive soft tissue damage and bone fractures, providing an ideal substrate for microbial colonization and biofilm formation. Moreover, the exigencies of military operations often preclude timely access to definitive surgical care and comprehensive infection control measures, exacerbating the risk of treatment failure and disease recurrence. The intense psycho-emotional stress of military personnel during combat and high-energy traumatic injuries sustained in battle often involve extensive soft tissue damage and comminuted bone fractures. All of this increases the area of secondary necrosis in tissues due to lipid peroxidation, creating an ideal environment for microbial colonization and biofilm formation. Additionally, urgent military operations often hinder the stages of medical evacuation and prolong the time from injury to the provision of highly skilled medical care and a full range of infection control measures to the injured, increasing the risk of treatment failure and disease recurrence.

As such, the management of musculoskeletal infections in military personnel demands a holistic approach encompassing early diagnosis, aggressive surgical debridement, and adjunctive therapies targeting biofilm eradication and antimicrobial stewardship. Suggested preventive measure then include early transport and treatment in specialized centers and antibiotic use restrictions, but a deeper understanding and more effective measures to mitigate the occurrence of MDR W-MSIs appear urgently needed. ■

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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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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: Nummer 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

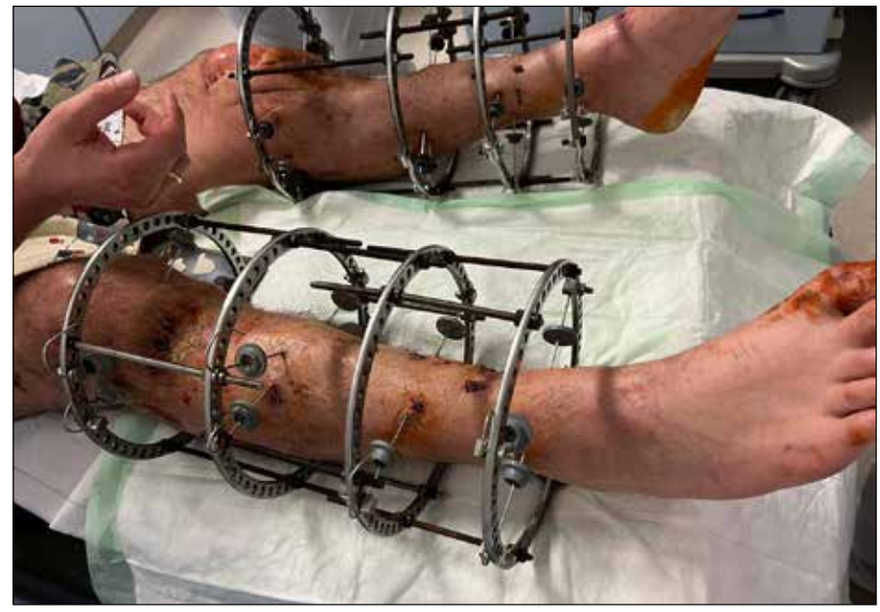

Figure 1: Patient with multiple injuries to the lower extremities and multiple small wounds

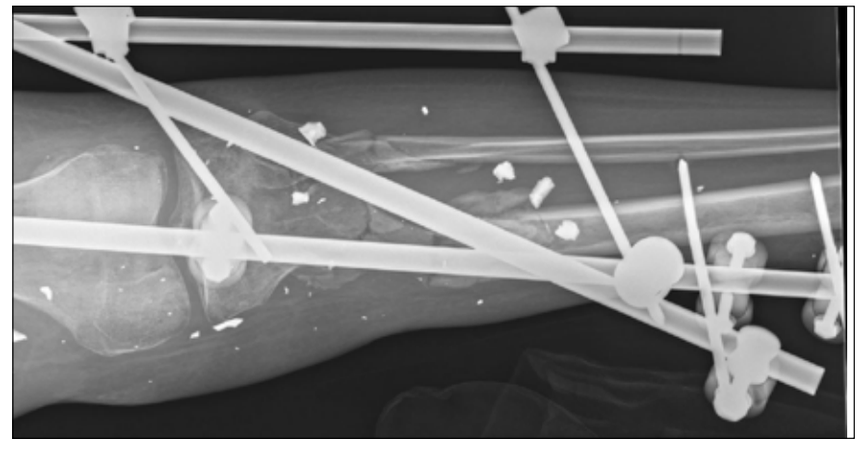

Figure 2: The a.p. radiograph of the right lower leg of the same patient showing multiple foreign fragments

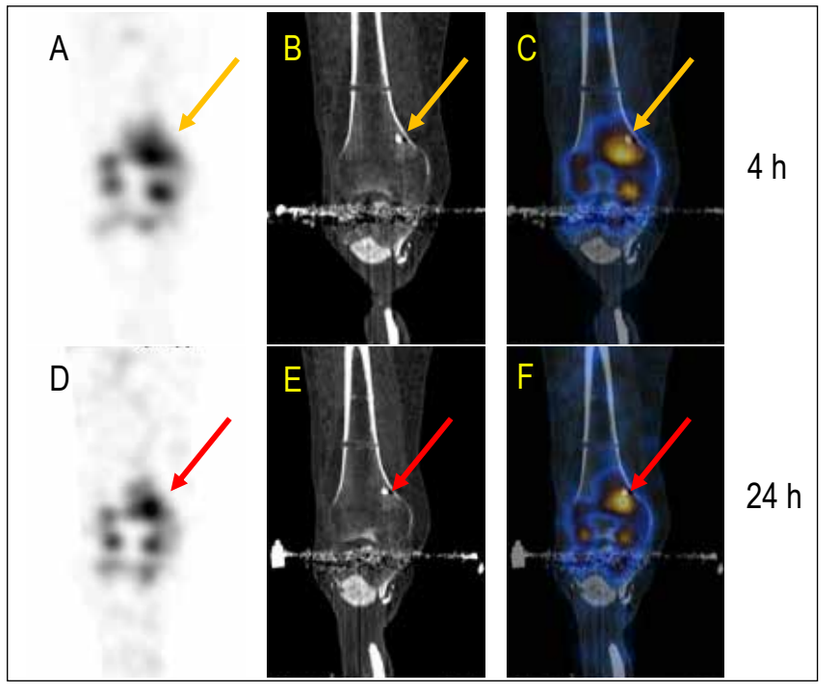

Figure 3: Anti-granulocyte antibody (AGA)-SPECT/CT presented an increased accumulation of granulocyte antibodies over time (orange arrows 4 h p.i., red arrows 24 h p.i.) in the medial femoral metadiaphysis adjacent to a radiopaque foreign body as an expression of an infected fragment. SPECT/CT with 99mTc-labelled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

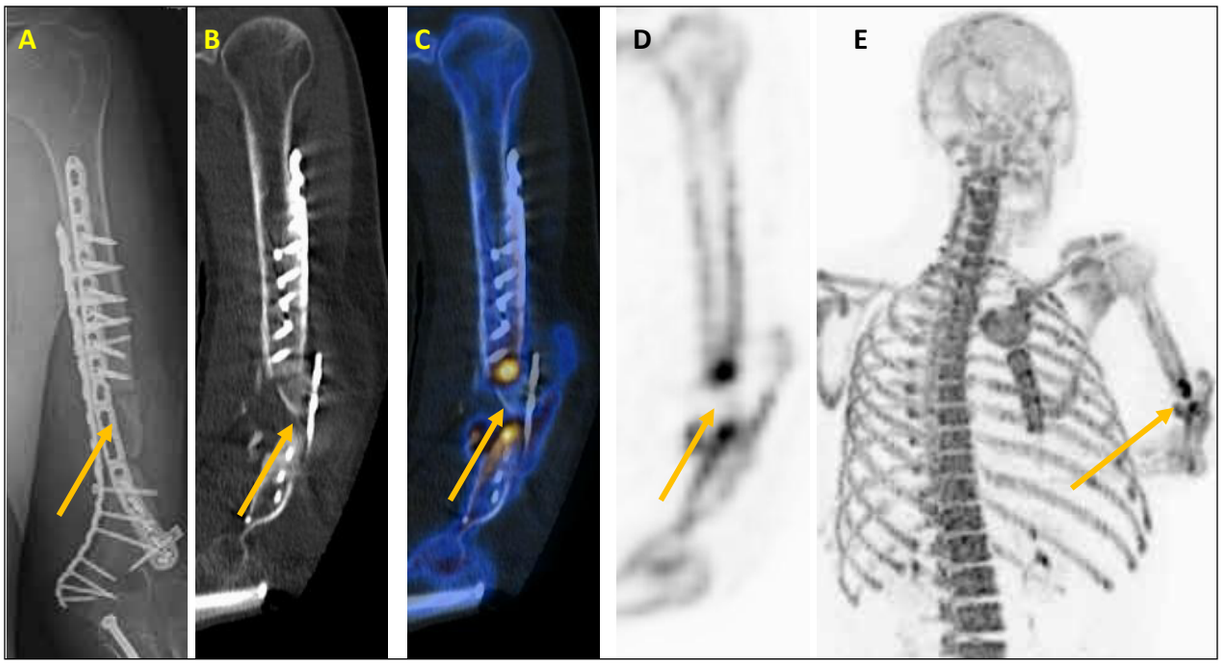

Figure 4: A radiograph of the left humerus showed a delayed union after bone chip implantation (orange arrow), corresponding Na[18F]F-PET/CT images (B-E) with coronal oblique view of the left humerus in the CT (B), fused PET/CT (C) and in the PET (D,E) present almost no tracer accumulation in the bone 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.

surroundings. This corresponds to an infection. Many other foreign bodies do not have this accumulation and are therefore not infected.

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.

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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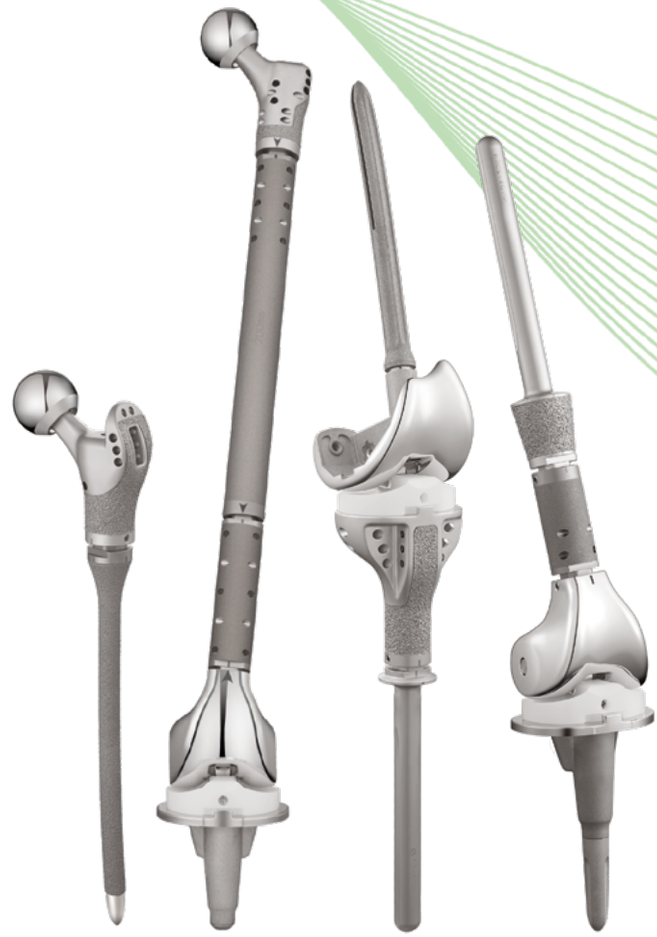

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MICROBIOLOGICAL VS. HISTOLOGICAL EXAMINATIONS IN SEPTIC ARTHRITIS OF THE KNEE JOINT: A COMPARATIVE ANALYSIS

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INTRODUCTION

According to international recommendations, therapeutic joint injections are considered an effective method of conservative treatment for osteoarthritis [1-4]. Hydrocortisone was introduced for intra-articular injection in 1951. Since then, vast experience has confirmed the value of this agent and of other corticosteroid suspensions for combating pain and inflammation when injected into the joint in patients with rheumatoid arthritis and other inflammatory arthropathies [5]. Despite the lack of serious long-term clinical evidence in the literature, intra-articular injections of steroid preparations are a common practice in conservative treatment of osteoarthritis [1-4, 6-8]. Risk factors include pre-existing joint diseases like rheumatoid arthritis, alcoholism, diabetes, skin ulcers, intravenous drug abuse, and immunosuppression. There are also iatrogenic factors associated with improper intra-articular injection techniques, breach of asepsis and antisepsis, where the most common etiological agent is Staphylococcus aureus (S. aureus) [9-11]. Marco Mattia Largi et al. (2022) in their retrospective study of post-injection septic arthritis found more frequent involvement of Staphylococcus aureus, and sometimes coagulase-negative staphylococci and anaerobes as bacterial culprits [12]. Similar data were also reported by other authors [13,14,15]. In their work, Mohamed M. et al. (2019) showed that out of 11 septic arthritis cases post intra-articular injections, the microorganism identified in cultures was Streptococcus mitis (three patients) and all other organisms represented oral flora. In five patients, the microorganism was not identified in cultures [16]. The risk of iatrogenic septic arthritis has been estimated at 0.005% and 0.0002% for joint injections [17].

Although potentially any joint after injection is prone to infection, the most commonly affected joint, in approximately 50% of cases, is the knee joint, followed less frequently by the hip, shoulder, and elbow joints [9-11, 17-19]. Delayed diagnosis or suboptimal treatment is associated with irreversible joint damage and permanent disability, with about a 10% mortality rate and significant morbidity [22]. One of the most important conditions for treating osteoarthritis after hydrocortisone injection into the knee joint is joint immobilization. As recommended by David H. Neustadt (2006), after a corticosteroid injection in the knee, the patient should remain in bed or at rest and walk as little as possible for three days, preferably only for needs such as bathroom and meals. After this period, crutches should be used in a three-point gait to protect the injected knee during walking for the next 2 to 4 weeks. A cane can be used if crutches are inappropriate or uncomfortable. This regimen prevents overworking the joint and delays steroid absorption systemically, thus optimizing therapeutic benefits [23].

Enhanced lipid peroxidation in joint tissues can contribute to the development of necrosis with subsequent septic joint inflammation. During movement, hydrostatic pressure increases significantly in inflamed human knee joints, causing intra-articular hypoxia. After movement, lipid and immunoglobulin oxidation occurs in the joint. Peroxidation of lipids in synovial fluid is not detected in resting knees. Synovial membrane reperfusion occurs after cessation of physical activities [24].

There are reports in the literature about studies such as arthrocentesis biopsies in arthritis cases [25]. In other works, histological studies of joint tissues in septic arthritis were carried out in an experiment [26].

In their systematic review, C.J. Mathews et al. (2007) identified 3291 studies devoted to septic arthritis [27]. However, none of these studies included histological examinations of knee joint tissues, let alone comparative histological examinations between steroid-induced and non-steroid-induced arthritis cases. It is well known that histological analysis is the gold standard for confirming a diagnosis. In our previous study, we found certain differences in the results of microbiological studies in septic arthritis of the knee joint with steroid-induced etiology and septic arthritis cases of non-steroid-induced etiology. Therefore, our goal was to determine how steroid preparations affect tissue morphology in septic arthritis of the knee joint and compare the obtained data with the results of microbiological analyses in the patients under study.

MATERIALS AND METHODS

A retrospective study was conducted involving 54 patients with septic arthritis of the knee joint (39 males, 15 females; average age: 43.8±4.9; range 5 to 77 years) who were treated at our clinic from 2010 to 2019. Seven patients (13%) were treated conservatively, while 47 (87%) underwent surgical treatment.

Samples for morphological studies were taken from 12 patients who underwent surgical treatment (25.5%), of which 10 were male (83.3%) and 2 were female (16.7%). The average age of the patients was 41.8±3.7 years (min. 5, max. 77). The average disease duration was 55 days (min. 5 days, max. 150 days).

The patients were divided into two groups based on septic and steroid etiology (following steroid administration into the joint), and each group was further divided into two subgroups: arthritis (without bone tissue involvement) and osteoarthritis (with bone tissue involvement according to radiological examinations). The results of both groups were compared. All patients were treated at a clinic in Baku, Azerbaijan. According to etiological factors, the patients were distributed as follows (see Table 1).

Diagnoses were confirmed by clinical, radiological, and other methods of examination and classified according to criteria described by J. H. Newman (1976) [28], with some modifications, as follows:

1. Septic arthritis without bone tissue involvement:

- positive cultures isolated from synovial fluid or material obtained during surgery (Group A);
- negative cultures, but purulent drainage from the knee joint (Group B);
- negative cultures, but pronounced clinical signs of local inflammatory process correlated with laboratory data (Group C);

Etiology of the infection	All septic arthritis (%)
After injury	19 (35.2)
Hematogenous	7 (12.9)
Steroid *(infections associated with intra-articular injection of the steroid drags)*	14 (25.9)
Postoperative	5 (9.3)
Other or unknown etiology	9 (16.7)

Table 1. Etiology of septic arthritis of the knee joint (n=54).

2. Septic osteoarthritis with bone tissue involvement based on radiological examinations:

- positive cultures from synovial fluid or material obtained during surgery (Group D);
- negative cultures, but pronounced clinical signs of local inflammatory process correlated with laboratory data (Group E) (Table 2).

Microbiological samples were obtained by joint puncture for synovial fluid collection and wound swab during surgery. Materials for histological analyses were obtained only during the surgery. Resected ends of the femur and tibia bones were placed in formalin solution and sent to the laboratory of pathology for analysis. The samples were analyzed using standard histological methods. Sections of each case were stained with hematoxylin and eosin. The samples were examined using an Axio microscope (Carl Zeiss, Germany) at 400x magnification, and photos were taken with a Scope 1 microscope (Zeiss, Germany).

Statistical data processing was carried out using the computer program Statistica 12.5. The results are presented in the form of M±SD, where M represents the mean, SD represents the standard deviation, and were calculated using an online calculator.

Existing clinical and radiological data were taken into account for lesion categorization. The study was conducted in accordance with the Helsinki Declaration, and the protocol was approved by the Ethics Committee. Given the retrospective nature and anonymity of the study, patient consent for using their data in the analysis was not required.

RESULTS OBTAINED

The causes of septic arthritis are shown in Table 1. It is worth noting that 25.9% of infections were a result of intra-articular steroid injections, and 9.3% followed surgeries. According to Newman's criteria, 40 (74%) patients did not show radiographic signs of bone lesions; specifically, 31 (57.4%) were classified as infections in Group A, 4 (7.4%) as infections in Group B, and 5 (9.2%) as infections in Group C. Among the remaining patients, 12 (22.2%) were identified as infections in Group D and 2 (3.7%) as infections in Group E.

Mixed flora, consisting of two microorganisms, was found in 17 cases (54.8%),

Arthritis	All arthritis	All osteo arthritis	SSA	SSOA	SA	SOA
n=54	n=40	n=14	n=9(16,7%)	n=5(9,2%)	n=31(57,4%)	n=9(16,7%)
group A	31 (77.5%)		3 (33.3%)		28 (90.3%)	
group B	4 (10%)		2 (22.2%)		2 (6.5%)	
group C	5 (12.5%)		4 (44.5%)		1 (3.2%)	
group D		12 (85.7%)		3 (60%)		9 (100%)
group E		2 (14.3%)		2 (40%)		-

Table 2. Newman criteria for diagnosing septic arthritis.
SA - septic arthritis; SSA - steroid-induced septic arthritis; SOA - septic osteoarthritis; SSOA - steroid-induced septic arthritis.

Clinical groups	Number of patient	Results of microbiological examinations					
		Patients treated by conservative method (n=7)			Patients who underwent surgical treatment (n=47)		
		Monoculture	Polymicrobial culture	Negative culture	Monoculture	Polymicrobial culture	Negative culture
		Quantity (%)	Quantity (%)	Quantity (%)	Quantity (%)	Quantity (%)	Quantity (%)
SSA	9	-	-	-	2 (22.2)	1 (11.1)	6 (66.7)
SSOA	5	-	-	-	-	3 (60)	2 (40)
SA	31	5 (71.4)	2 (28.6)	-	5 (20.8)	16 (66.7)	3 (12.5)
SOA	9	-	-	-	-	9 (100)	-
Representativeness error (M±SD)					3.5±2.1	7.3±6.8	3.7±2.1

Table 3. Results of microbiological studies (n=54).
SA - septic arthritis; SSA - steroid-induced septic arthritis; SOA - septic osteoarthritis; SSOA - steroid-induced septic arthritis.

and infections with three microorganisms were found in 14 cases (45.2%).
In patients with septic arthritis (SA), positive cultures were identified in 90.3% of patients. 100% of patients with septic osteoarthritis (SOA) had positive cultures, exclusively in the form of mixed flora. In patients with steroid-induced septic arthritis (SSA), cultures were positive in 33.3% of patients. Positive cultures were found in 60% of patients with steroid-induced septic osteoarthritis (SSOA) (Table 3).

The analysis of histological sections yielded the following results: Paralytic dilated sinusoidal capillaries, intravascular stasis, and vascular edema were observed in all histological samples. In arthritis of steroid etiology, a large amount of lymphoplasmacytic and neutrophil infiltrate around sinusoidal-type vessels is observed (Figure. 2 B), eosinophilic leukocytes (Figure 4 A), necrotic granulomatous foci of inflammation, areas of hemorrhage, and giant multinucleated macrophages (Figure 1 B). During an acute inflammatory reaction, a large number of neutrophils, leukocytes, individual lymphocytes, and plasma cells were observed (Figure 2 A). In SA, multiple lymphoplasmacytic infiltrations, fibrosclerotic changes, multinucleated giant cells - Langhans-type cells, and granulomatous foci of inflammation accompanied by areas of hemorrhage were observed (Figure 1 A).

Destructive changes are more noticeable in osteoarthrosis. In the case of SOA, cartilage tissue samples show proliferation with foci of destruction (Figure 6 A). The same foci of destruction are evident against the background of normal car-

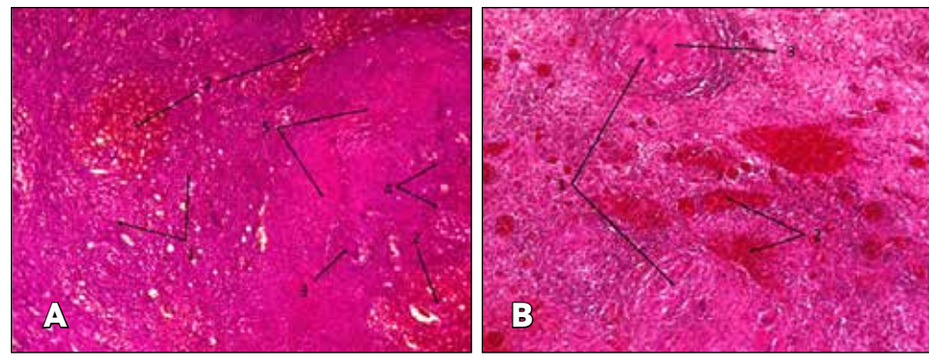

Figure 1. A (SA) 1 - multiple lymphoplasmacytic infiltration, 2 - areas of hemorrhage, 3 - multinucleated giant cell (Pirogov-Langhans cells), 4 - foci of granulomatous inflammation, 5 - fibrosclerotic changes;
B (SSA) 1 - foci of granulomatous inflammation (non-necrotic), 2 - areas of hemorrhage, 3 - multinucleated giant cells macrophages. (400x magnification, hematoxylin-eosin staining).

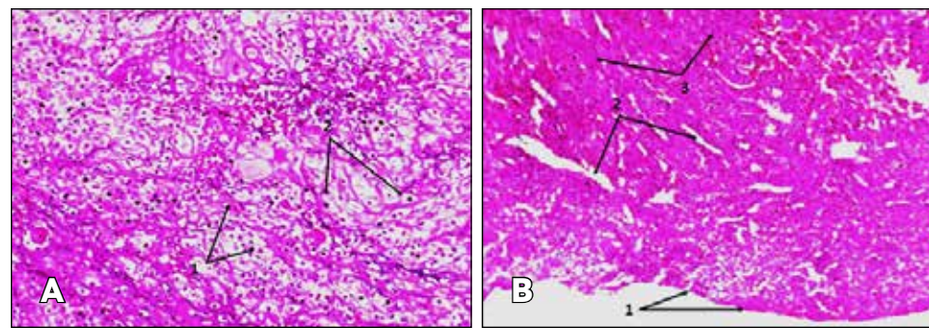

Figure 2. (SSA)
A. (acute inflammatory process) 1 - massive number of neutrophils and leukocytes, 2 - single lymph and plasmocytes;
B (synovium) 1 - border of the synovial membrane, 2 - sinus type vessels, 3 - numerous lymphoplasmacytic and neutrophil infiltration (around sinus-type vessels). (400x magnification, hematoxylin-eosin staining).

tilage tissue (Figure 7 B). In bone tissue samples, sequestra surrounded by a large number of neutrophils and leukocytes are noted, along with lymphoplasmacytic infiltration (Figure 5 A).

In SOA, we observe vessel wall destruction, lymphoplasmacytic infiltration, vascular fibrosclerotic changes, signs of hyperemia (numerous capillaries), fibrosis of adipose tissue, formation of bone sequestra, and multiple neutrophils and leukocytes (Figures 4 B, 5 A).

In the case of SSOA, destructive foci are observed in the cartilage tissue samples, primarily with plasma cells that, in some areas, penetrate into the normal cartilage tissue (Figure 6 B). SSOA is accompanied by the formation of bone sequestra surrounded by a large number of neutrophils and leukocytes. Lymphoplasmacytic infiltration is present, and dilated sinus-like vessels filled with blood are visible (Figire 7 A).

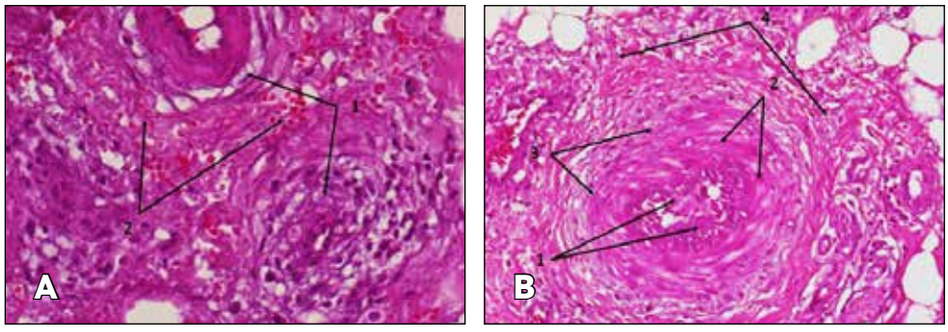

Figure 3. (SA)
A 1 - infiltration lymphoplasmacytic around the vessel, 2 - areas of hemorrhage (erythrocytes entered the stroma),
B (artery - during a slow-moving inflammatory process) 1 - destruction of the arterial vessel, 2 - mild lymphoplasmacytic inflammation, 3 - breakdown of collagen fibers, 4 - mild inflammation of the stroma around the vein. (400x magnification, hematoxylin-eosin staining).

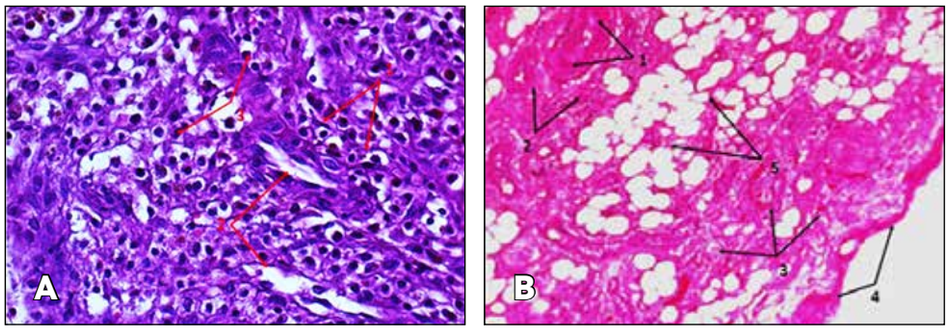

Figure 4. (SSA)
A 1 - massive lymphoplasmacytic infiltration, 2 - sinus type vessels, 3 - eosinophilic leukocytes;
B (SOA) 1 - destruction of the vascular wall, lymphoplasmacytic infiltration, 2 - vascular fibrosclerotic changes (a small number of inflammatory infiltrations), 3 - numerous capillaries (a sign of hyperemia), 4 - synovium, 5 - fibrous adipose tissue. (400x magnification, hematoxylin-eosin staining).

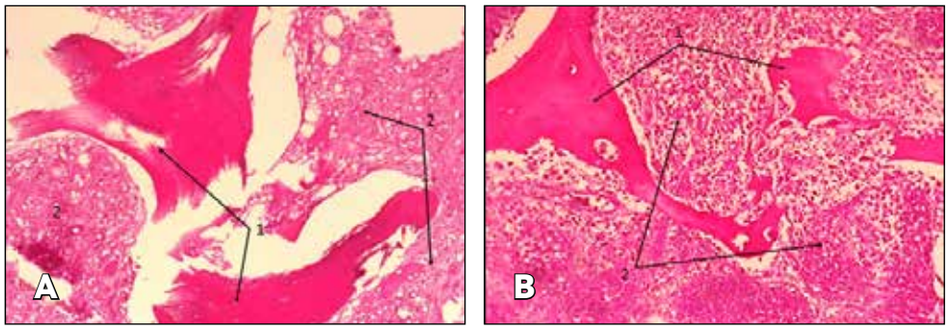

Figure 5. Bone tissue:
A (SOA) 1 - bone sequestrum, 2 - area of inflammatory infiltration in bone tissue;
B (SSOA) 1 - bone sequestrum, 2 - large-scale neutrophils, leukocytes, lymphoplasmacytic infiltration (covers sequestrum). (400x magnification, hematoxylin-eosin staining).

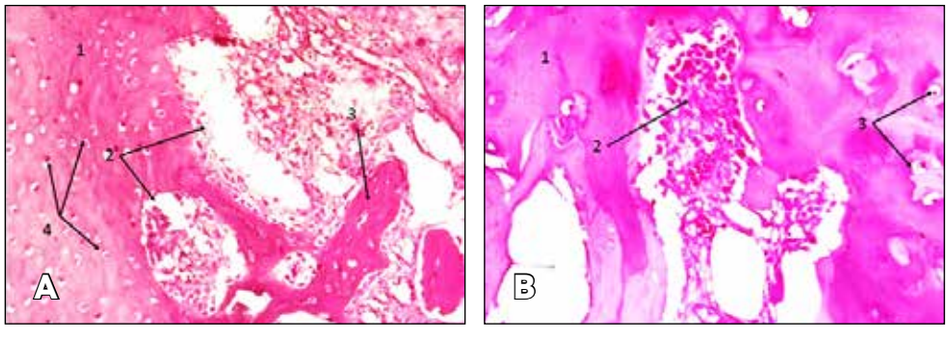

Figure 6.
A (SOA) 1 - cartilage tissue, 2 - foci of destruction, 3 - bone tissue, 4 - proliferating chondrocytes;
B (SSOA) 1 - cartilage tissue, 2 - destruction area that affects cartilage tissue (consists mainly of plasmatic cells), 3 - normal chondrocytes. (400x magnification, hematoxylin-eosin staining).

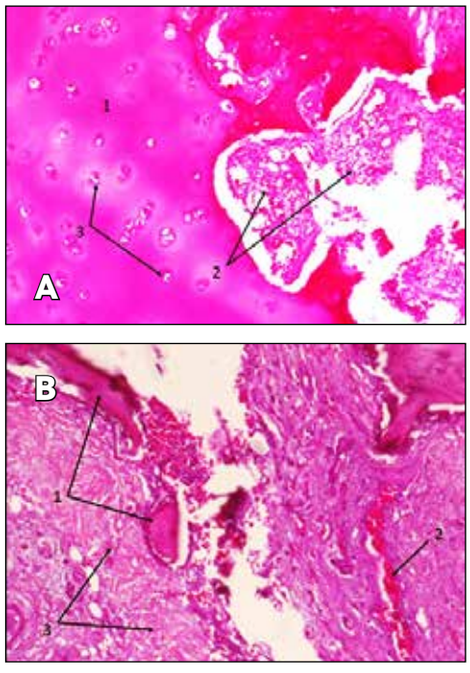

Figure 7.
A (SOA) 1 - normal cartilage tissue, 2 - destruction area that affects cartilage tissue, 3- chondrocytes;
B (SSOA, bone tissue) 1 - bone sequestrum, 2 - paralytic dilated sinus-type capillaries (intravascular stasis is present, vascular fullness is observed), 3 - mild lymphoplasmacytic inflammation. (400x magnification, hematoxylin-eosin staining).

DISCUSSION

Positive results of microbiological analysis were obtained in 90.3% of patients. Approximately similar figures for SA are reported as follows: Camilo, P.H. et al. (2014) - 91.8%, Chao-Ming, C. et al. (2013) - 85.9%, and others [29,30].

According to our data, Staphylococcus aureus was detected in 29.1% of patients either as a monomicrobial infection or in associations. Other authors have also reported high rates of Staphylococcus aureus isolation in microbiological analyses [29,30,31].

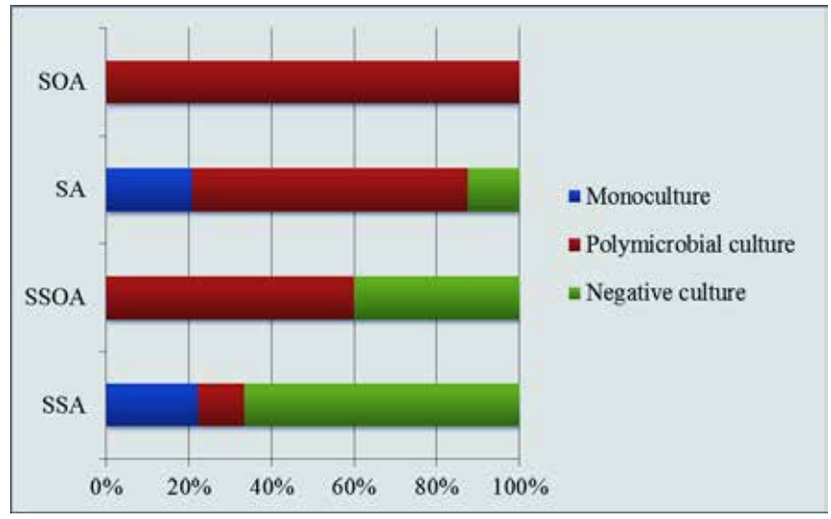

Figure 8. Results of bacteriological studies by groups.

In 66.7% of patients with SSA, the microbiological study results were negative, despite the fact that the inflammatory process was in an acute phase, as confirmed by clinical and laboratory indicators. It can be assumed that in this group of patients, the inflammatory process is aseptic. Positive results of microbiological analysis were obtained in 60% of patients with steroid-induced septic osteoarthritis (SSOA). In Figure 8. The results of microbiological cultures in various groups of SA are given.

When analyzing the data of microbiological analyses in patients with SOA and SSOA, it can be noticed that associations of microorganisms are observed in them. This indicator was 100% in patients with SOA and 60% in patients with SSOA. It can be assumed that the chronization of the septic process contributes to this. As for the large number of negative results in microbiological analyses in patients with SSA and SSOA, it is definitely challenging to answer these interesting data. Here, data from Á J Geirsson et al. (2008) can be cited, which noted that 39% of children with a clinical picture of septic arthritis had negative results in synovial fluid and blood cultures. Clinical and laboratory characteristics were similar in children with positive and negative cultures [17]. The authors note that the results are identical to numerous other reports, and to date, no reasonable explanation has been proposed [32-36].

According to our data, 66.7% of patients with SSA had negative results in microbiological studies. It can only be assumed that an inflammatory process is proceeding in an aseptic scenario in them. Steroid preparations may be responsible for such joint destructions. A study by Chao-Ming, C. et al. (2013) showed that the results of treating SSA did not differ from the results of treating SA with non-steroidal etiology [30]. On the other hand, data obtained by Choudhry, M.N. et al. (2016) in their systematic review showed that the introduction of steroid preparations into the joint within a few hours leads to a very high level of sugar in patients with diabetes [37]. Thus, steroid preparations may somehow influence the tissues of the knee joint.

The histological analysis data we obtained somewhat confirm this. Cellular infiltration was detected in all groups. However, in patients with SSA and SSOA, it was relatively moderate. Similar results have been published in the literature on experimental arthritis [38]. Neutrophils, leukocytes, lymphocytes, lymphoplasmacytic infiltration, paralytic dilated sinus-like capillaries, intravascular stasis, vascular fullness, and fibrosclerotic changes were found in all patients, but no significant differences between groups were found. The morphology of SA, regardless of etiology, is usually similar and is usually accompanied by significant destruction of all joint components. In the background of steroid administration, this process becomes more acute, especially noticeable when examining cartilage tissue. For example, in the case of SOA, cartilage specimens show proliferation with foci of destruction. In the case of SSOA, destructive foci, mainly with plasma cells, penetrated normal cartilage tissue in some areas (Figure 6B). SSOA is characterized by the formation of bone sequester, surrounded by a large number of neutrophils and leukocytes.

Thus, in steroid arthritis, the thickness of cartilage tissue was less compared to the other group, and the depth of the destruction site was greater. Getmanets, A.V. (2012) observed similar results in creating experimental arthritis in animals [26]. Comparing the data of morphological and microbiological studies, it can be suggested that the introduction of steroid preparations into the joint possibly initially causes changes in joint tissues that lead to cell necrosis of soft tissues with the development of an aseptic inflammatory process. This may occur as a result of disrupting POL processes, which intensify with the introduction of steroid preparations [39]. With repeated intra-articular steroid injections, the percentage of such necrosis can significantly increase [40]. M Suntiparpluachac et al. (2016) suggest that corticosteroids increase oxidative stress and alter the expression of genes such as cyclin-dependent kinase inhibitor 1A, growth differentiation factor 15, and c-Fos, which are involved in cell death and chondrotoxicity [41]. Pattaranatcha Charnwichai et al. (2023) also show that TA induces chondrotoxicity by enhancing oxidative stress and altering gene expression involved in cell death. The authors studied and compared histological analyses of materials obtained from patients undergoing knee joint arthroplasty. They showed that in patients who received intra-articular corticosteroid injections six months before the operation, a decrease in the thickness of articular cartilage was noted. The same decrease in articular cartilage thickness was noted in our study [42]. Indirectly, the high number of negative microbiological analyses in patients in the acute phase of SSA - 66.7%, speaks to the primacy of aseptic cell necrosis.

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In conclusion, it can be said that all morphological changes characteristic of purulent-inflammatory processes were found in both groups and that they were comparable in histological characteristics. Further, more in-depth clinical-experimental studies are needed to accurately establish the morphological changes specifically related to steroid arthritis.

CONCLUSION

1. Positive results in patients with SA were 90.3%, in SSA - 33.3%, in SOA - 100%, and in SSOA - 60%.

2. Staphylococcus aureus (29.1%) was the most commonly encountered microorganism overall.

3. Histological studies of joint tissues in SA showed that all components of the joint were affected.

4. In both SOA and SSOA, all morphological changes characteristic of purulent-inflammatory processes were observed. Against the background of steroid preparations, this process becomes more acute, especially evident when examining cartilage tissue. Its thickness was less compared to the other group, and the depth of the destruction site was greater, affecting even the subchondral tissue.

5. It can be assumed that in acute SSA, the inflammatory process initially starts and proceeds along an aseptic scenario, which is indirectly indicated by the low number of positive microbiological analyses (33.3%).

Limitation of the article: All data in the article are retrospective and non-randomized. For a more reliable statistical analysis, studies on a larger number of patients are necessary. Some assumptions made by the authors need to be verified by studying relevant biochemical processes in a large number of patients.

Conflict of interests: The authors, their closest relatives, and any research funds they are associated with have not received any financial payments or other benefits from any commercial organization related to the subject of this article.

Statement: This statement certifies that all authors have reviewed and approved the manuscript presented. We guarantee that the article is the original work of the Authors. We guarantee that the article has not been previously published and is not under consideration for publication elsewhere. The corresponding author bears full responsibility for the submission on behalf of all co-authors.

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PREVALENCE OF ORTHOPAEDIC SURGICAL SITE INFECTION IN EGYPT

A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

Surgical site infection (SSI) remains a significant and challenging complication following orthopedic surgeries, impacting patient outcomes and healthcare systems globally [1]. These infections, which occur at the site of surgery within 30 days postoperatively or within a year if an implant is placed, pose a serious threat due to the intricate nature of orthopedic procedures and the complex environments in which they are performed [2]. Orthopedic SSIs can lead to extended hospital stays, increased medical costs, additional surgical interventions, and, most critically, substantial morbidity and mortality among patients [3].

The prevalence of SSIs in orthopedic surgeries varies widely, influenced by factors such as the type of surgery, patient comorbidities, surgical techniques, and adherence to infection control protocols [4]. Common pathogens responsible for these infections include Staphylococcus aureus, including methicillin-resistant strains (MRSA), coagulase-negative staphylococci, and Gram-negative bacilli [5]. The advent of antibiotic-resistant organisms further complicates the management and prevention of SSIs in orthopedic settings [6].

Preventive measures are multifaceted, involving preoperative, intraoperative, and postoperative strategies [7]. Preoperative measures include optimizing patient health, controlling blood glucose levels, and appropriate antibiotic prophylaxis [8]. Intraoperatively, meticulous surgical technique, proper sterilization of instruments, and maintaining normothermia are crucial [4]. Postoperative care involves wound management, timely removal of drains and catheters, and vigilant monitoring for early signs of infection [9].

Despite advances in surgical techniques and infection control practices, the incidence of SSIs in orthopedic surgeries remains a pressing concern. Ongoing research and the development of innovative strategies are essential to reduce the burden of these infections and improve patient outcomes in orthopedic care.

METHODS

The procedural framework of this investigation adhered to the methodology outlined in the Cochrane Handbook for Systematic Reviews and Meta-analysis [10]. We followed the PRISMA statement guidelines in reporting this meta-analysis [11].

1. Literature search

We conducted a methodical search across the subsequent databases: PubMed, Scopus, Web of Science (WOS), and Embase, aiming to retrieve relevant published studies from their inception until June 2024. We used keywords to build our search strategy including ("Surgical Wound Infection"[Mesh] OR "Surgical Site Infection" OR "SSI" OR "Postoperative Infection") AND ("Prevalence" OR "Epidemiology" OR "Incidence" OR "Rate") AND ("Egypt" OR "Egyptian"). All duplicates were removed by Endnote software.
Rayyan software [12] was utilized during the selection process, with two reviewers independently and blindly assessing the retrieved references in a two-stage procedure. First, they screened the titles and abstracts of all extracted articles. In the second phase, they conducted a thorough full-text screening of all eligible abstracts. Any discrepancies were resolved with the assistance of a third reviewer.

2. Selection and Eligibility criteria

In selecting relevant studies, we followed a specific set of criteria. This investigation focused on patients undergoing any type of orthopedic surgery without interventions or comparators, with the primary outcome being the incidence of surgical site infections (SSIs). We excluded non-English studies, case reports, animal studies, reviews, editorials, studies with only an abstract or unavailable full text, or overlapping data.

3. Data Extraction

Data from eligible studies was gathered on a standardized sheet for data extraction form by two independent reviewers. Then a cross-verification was conducted, and any discrepancies were addressed through discussion. The uniform data extraction sheet encompasses two domains, from which details related to the included studies are derived, first domain was: characteristics of included studies such as (study ID, Study design, Country, Number of centers, inclusion criteria, number of patients, follow-up duration and conclusion). The second domain included the outcomes that we highlighted on them previously.

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4. quality assessment

Two authors independently evaluated the Risk of bias using the Joanna Briggs Institute (JBI) critical appraisal tools [34]. The suitable checklist was selected based on the observational study type. Each checklist included various questions that could be answered with "yes," "unclear," "no," or "not applicable." Discrepancies were resolved through consensus. Studies were categorized as having a low, medium, or high risk of bias according to the relevant questions. [13]

5. Statistical analysis

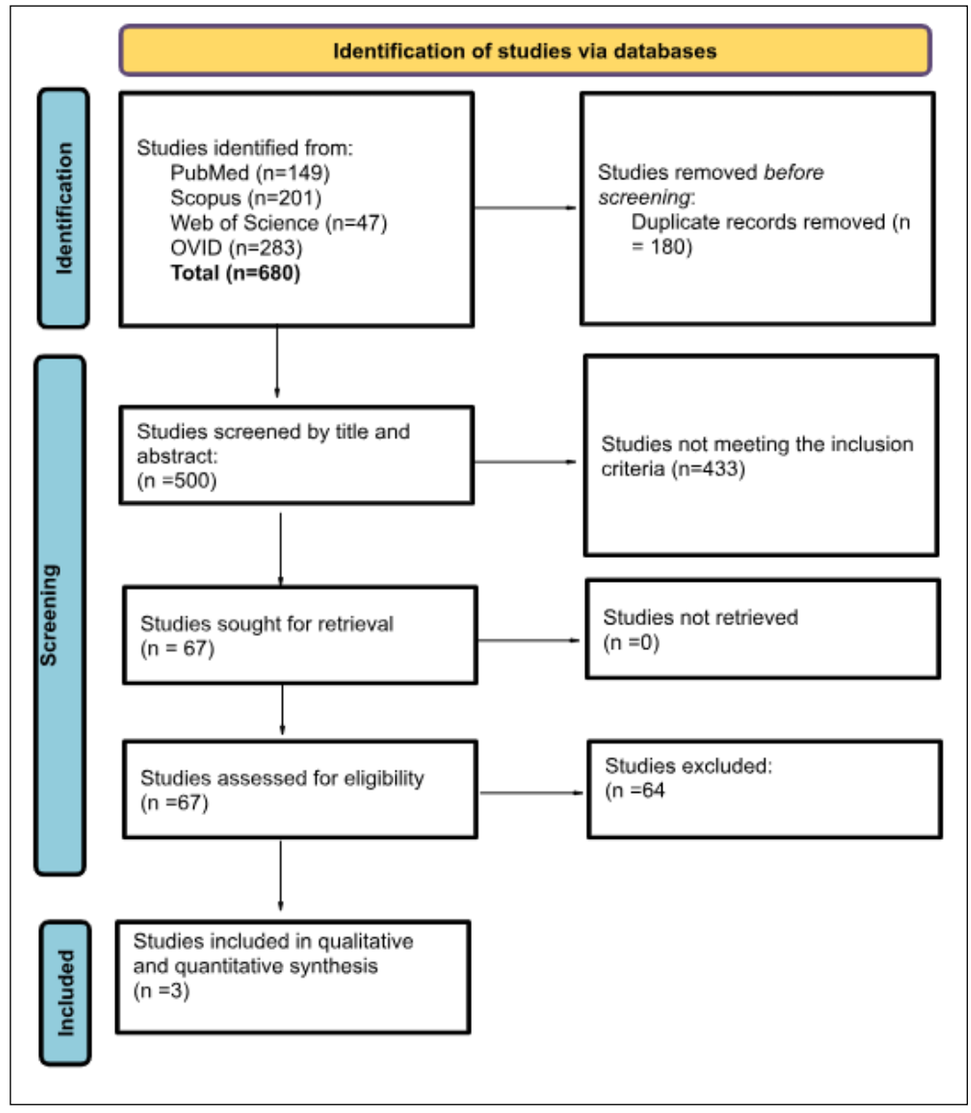
For comprehensive analysis of extracted data, we used OpenMeta[Analyst] software tool for analysis and construction of forest blots; For dichotomous outcomes, we pooled them as Risk ratio (RR) and their corresponding 95% confidence interval (CI) using the Mantel-Haenszel method, we also performed sensitivity analysis to solve the heterogeneity.

Additionally, to assess statistical heterogeneity among the included studies, a visual inspection of the forest plots was conducted. The Chi-square test (Cochrane Q test) and the Higgins and Thompson I^2 statistic were also used to quantify heterogeneity, with the formula $I^2 = ((Q - df) / Q) \times 100\%$. If the I^2 value exceeded 50% and the Chi-square test's p-value was less than 0.1, significant statistical heterogeneity was considered present between the studies. In such cases, DerSimonian and Laird random effects models were applied to address the heterogeneity effectively.
On the other hand, heterogeneity would be fluctuated as low, moderate, and high whether I2 valued as < 25%, from 25-75%, or > 75%, respectively. [14]

RESULTS

1. Search Results and Study Selection

680 publications were found by scanning the various electronic databases (PubMed, Web of Science, Scopus, and Ovid). 180 articles were discovered to be duplicates and deleted. Through the application of the above-described inclusion and exclusion criteria, 677 studies were deemed irrelevant and subsequently eliminated throughout the screening process. Ultimately, it was determined that three studies [15–17] qualified and were included in the analysis. (Figure 1)



2. Characteristics of Included Studies

All the included studies were carried out in Egypt including one prospective analytical study, one single institution study, and one cross-sectional study (Table 1). The follow up duration was different among these studies ranging from three to nine months.

3. Quality assessment of the included studies

Two studies were classified as having medium concerns regarding the methodological quality and one study, Kotb et al 2019, demonstrated a weak adherence to methodological guidelines and high risk of bias, which decreased the validity of its findings. (Table 2 and 3)

4. Prevalence of surgical site infection in orthopedic patients

The analysis of SSI revealed that its incidence is statistically significant (P value < 0.05) with a risk ratio (RR) = 0.224 and 95% confidence interval (CI) [0.125; - 0.323. with significant heterogeneity I^2=81.09. (Figure 2)

5. Sensitivity analysis on prevalence of surgical site infection in orthopedic patients

After removal of the study Afifi 2010 [15] the heterogeneity was resolved I^2 = 0%. (Figure 3)

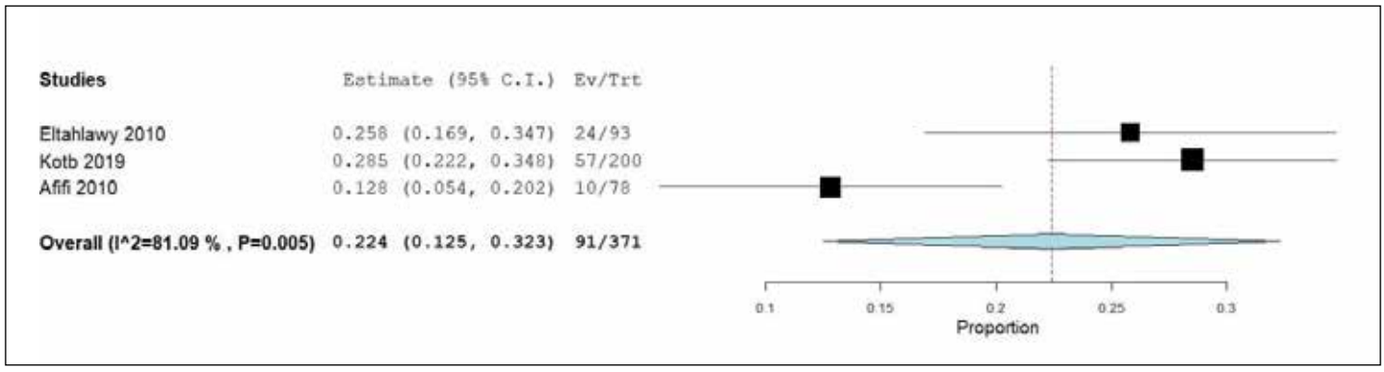


Figure 2. Forest plot showing prevalence of surgical site infection in orthopedic patients

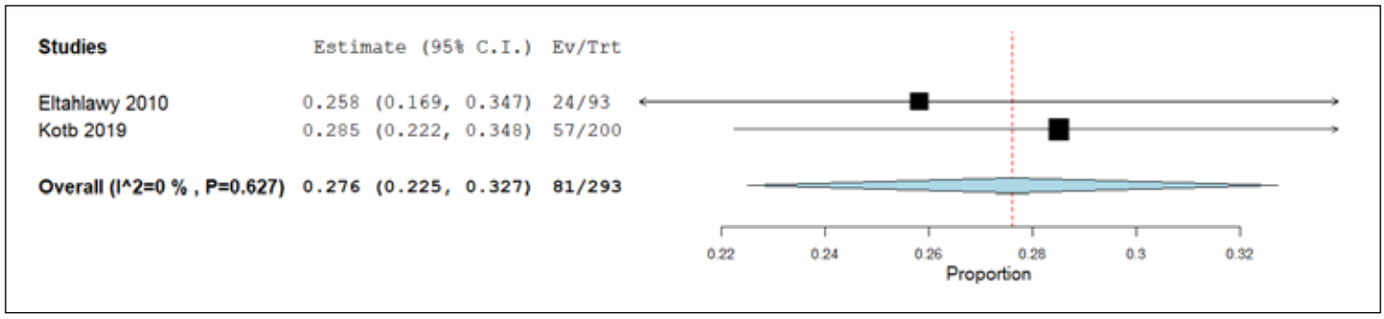


Figure 3. Forest plot after sensitivity analysis of prevalence of surgical site infection in orthopedic patients

Study ID	Country	Study design	Inclusion criteria	Number of centers	Number of patients	Follow-up duration	Conclusion
Afifi 2010	Egypt	Prospective Cohort	All patients undergoing surgical operations at orthopedic department, . Emergency cases were excluded.	1	121	90	The SSI incidence rate was 8.264%, with significant associations found for age >50 years, diabetes mellitus, ASA score >2, surgery duration >2 hours, and use of drains. The use of drains was the only independent risk factor. Common isolated organisms were *Staphylococcus aureus*, *Pseudomonas spp.*, and *E. coli* (20% each).
Abdel-Halim 2010	Egypt	Prospective Cohort	all patients undergoing surgical operations at orthopaedic department.	1	93	30	Incidence of SSIs in orthopedic patients in Egypt is higher than that reported in some developing countries. *S. aureus* is the most common pathogens associated with orthopedic SSIs
Kotb 2019	Egypt	Cross-sectional	Adult patients their age range between (18-65) years old from both sexes	1	200	-	Prevalence of orthopedic wound infection over three months was (28.5%). There was a positive correlation between dressing technique and wound infection

Table.1 Summary of the included studies.
SSI : Surgical site infection

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Category
Abdel-Halim 2010	Y	Y	Y	N	N	Y	Y	N	U	U	Y	Medium
Afifi 2010	Y	Y	Y	Y	N	Y	Y	N	U	U	Y	Medium

Table.2 Quality assessment of cohort studies
I: Not Applicable; N: No; U: Unclear, Y: Yes

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Category
Afifi 2010	Y	Y	Y	Y	N	N	N	Y	High

Table.3 Quality assessment of the cross-sectional study
I: Not Applicable; N: No; U: Unclear, Y: Yes

DISCUSSION

Surgical site infections (SSI) are the most common complications in surgical patients and the second most common complications in orthopedic patients leading to prolonged hospital stay, readmissions to the hospital, and increased morbidity and mortality [18, 19]. One of the most common challenges that orthopedic surgeons face is the use of implants for open reduction and internal fixation which are foreign objects to the body increasing the risk of SSI. [20]

The aim of this analysis is to estimate the incidence of SSI in orthopedic surgeries in Egyptian hospitals. The orthopedic procedures in the included studies were mainly internal fixation of fractures and arthroplasty.

Our findings estimated the incidence of SSI to range from 12.5% to 32.3%, with statistically significant results (RR = 0.224, 95% CI [0.125 to 0.323], $p < 0.05$].
In 2002, SSI was the second leading cause of healthcare-associated infections (HAI) in both the USA and Europe. In the USA, there were nearly 270,000 episodes per year, accounting for 20% of HAIs, while in Europe, there were approximately 900,000 episodes annually, representing 19.6% of HAIs [21]. A recent meta-analysis with a total of 43 studies from 29 countries no including Egypt aimed to estimate the global incidence of SSI [22]. The study found a worldwide SSI incidence rate of 2.5%, which is notably lower than the 5.6% reported by Allegranzi et al [23]. Moreover, according to Mengistu et al [22], the highest incidence of SSI worldwide was found in studies conducted in Africa, accounting for 7.2% [22]. This finding aligns closely with Allegranzi et al [23], which reported a pooled SSI incidence of 5.6% among patients in developing countries. Also, Ngaroua et al, which aimed to estimate the incidence of SSI in sub-Saharan Africa reported a pooled SSI incidence of 14.8% [24]. All these outcomes are lower than those reported in Egypt ranging from 12.5% to 32.3%.

Multiple risk factors could be attributed to this high-risk SSI. Male gender may be associated with high risk of SSI as proven by Al-Qurayshi et al and Utsumi et al [25, 26] this could be related to the fact that hormones may play a role in defining proper immune response where females have eminent cell-mediated immune responses compared with males owing to their low testosterone levels [27], also older patients between 17 and 65 years demonstrated higher risk for SSI, while patients aged 65 and above showed low risk of SSI by 1.2% for every year based on Kaye et al [28] which is inconsistent with Hegazy et al and Al-Mulhim et al that reported higher risk of SSI in younger patients [29, 30], but it could be due to the majority of patients in Al-Mulhim et al were reported to have traumatic injury and it has been shown that preoperative injury to soft tissues is a major risk factor for SSI. [30, 31]

Additionally, smoking significantly increases the risk of SSI as it is known for its negative effect on immunity causing impaired wound healing, wound dehiscence, and incisional hernia [32]. Sheet et al. highlights a growing concern about smoking in developing nations, where almost 80% of the world's 1.1 billion smokers live. Furthermore, additional risk factors such as obesity, duration of surgery, pre-existing infections, blood transfusions, low serum albumin levels, and inadequate sterilization practices may contribute to the high rate of SSIs in Egypt and other developing countries. [33, 34]

STRENGTHS AND LIMITATIONS

This is the first meta-analysis conducted to evaluate the prevalence of orthopedic SSI in Egyptian hospitals. A comprehensive search strategy was formulated and used to search different electronic databases to retrieve all relevant studies. This meta-analysis strictly followed the Cochrane Handbook guidelines, including only RCTs and having at least two authors involved in each step. This meticulous methodology enhanced the reliability of our findings and provided important insights into the prevalence of orthopedic SSI in Egypt. Nonetheless, our study encountered several challenges. The limited number of included studies and the small sample sizes hindered our ability to gather comprehensive data on the prevalence of SSIs in Egypt. Moreover, the three studies we included only covered patients from three hospitals in Egypt: Assiut, Tanta, and Cairo. There are several gaps in the surveillance of SSI including the lack of surveillance methodologies post-discharge (patients encountered some difficulty to assess their own wounds for infection), no data from many hospitals, and the absence or limited written guidelines on proper perioperative antibiotic policies.

A multicenter surveillance study, on many homogeneous Orthopedic cases with larger sample size and longer duration, is needed to allow for meaningful comparisons between different Orthopedic conditions and hospitals. ■

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A NATIONWIDE SURVEY OF TUMOR ENDOPROSTHESIS INFECTION IN JAPAN: HISTORY AND PROSPECTS

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INTRODUCTION

While oncological and functional outcomes of malignant bone and soft tissue tumors have significantly improved, perioperative complications remain a problem in tumor endoprosthesis reconstruction. Indeed, surgical site (SSI) and periprosthetic joint (PJI) infections result in significant difficulties for patients, such as devastating functional and economic loss as well as prolonged treatment.

The rarity of malignant bone and soft tissue tumors and the appreciable variation in patients' status, treatment modalities, and prevention/treatment modalities for SSI all make it difficult to establish reliable evidence for tumor endoprosthesis infection control. To date, robust and broad evidence has accumulated on SSI/PJI prevention and control in conventional arthroplasty. While the second international consensus meeting in 2018 recommended the application of this evidence for tumor endoprosthesis SSI/PJI [1], it remains controversial whether this evidence could be safely applied for managing SSI/PJI of tumor endoprostheses. Many cases are required to exclude confounding factors and establish durable statistical models via inferential statistics. The practical solutions for such intractable conditions include analyzing data from high-volume centers, multicenter studies, nationwide registries, and systemic reviews and meta-analyses. The first author has been engaged in several nationwide studies in this area. This article presents the history and status of the etiological studies for tumor endoprosthesis SSI/PJI in Japan.

HISTORY AND PERSPECTIVE OF NATIONWIDE SURVEYS

(Table 1, Figure 1)

1. JOA Project [2,3]

Until the early 2000s, most evidence on SSI was provided from general surgery cases [4]. Since the etiology, status, and risks of infection in orthopedic surgery had not yet been established at that time, especially in Japan, a nationwide etiological study focusing on SSI in orthopedic surgery was urgently needed. Founded in 1978 to promote the study of infectious diseases of the bones and joints, the Japanese Society for Study of Bone and Joint Infections (JSSBJI) had planned a nationwide retrospective etiological study on SSI in 2003. This study aimed to estimate the incidence and risk factors of SSI in primary joint arthroplasty and spinal instrumentation surgery performed in the Japanese Orthopaedic Association (JOA) -certified educational hospitals in 2004. This study was adopted into the academic project research of the JOA in 2005. It ultimately collected 9882 joint arthroplasty cases and 2469 spinal instrumentation cases. The incidence of SSI was 1.36% in joint arthroplasty and 3.73% in spinal instrumentation [3]. This survey's results were broadly quoted in the Clinical Practice Guideline on the Prevention of Surgical Site Infections in Bone and Joint, Second Edition (2015) in Japan [5]. This survey is considered the first nationwide study of SSI in orthopedic surgery in Japan. Unfortunately, it included a limited number of oncological cases. Among 83 cases undergoing oncological resection, seven (8.4%) were recorded as having SSI, whereas the incidence of SSI in osteoarthritis, bone necrosis, rheumatoid arthritis, and trauma cases were 1.3%, 1.1%, 1.2%, and 1.8%, respectively. Therefore, these findings support a higher incidence of SSI in tumor endoprosthesis reconstruction than in other conditions under the standardized definition of SSI.

2. Study of SSI at five referral hospitals

While the highest incidence of SSI in tumor endoprosthesis was confirmed in Japan, there remains a lack of specific data on SSI/PJI in tumor endoprosthesis. Therefore, five orthopedic oncology specialist hospitals planned a multicenter study on SSI in tumor endoprosthesis around the knee in 2008 [6]. That study collected data from 82 tumor endoprosthesis reconstruction cases with or without SSI. The incidence of deep infection was 17.0%. This study could collect information on independent variables, both tumor-specific factors (tumor origin, chemotherapy, bone resection length, extracapsular resection, and soft tissue status) and generally accepted factors specific for infection control (prophylactic antibiotics and operating time; Figure 2). At that time, lack of the gastrocnemius muscle flap to the anterior area of the prosthesis after tumor resection in the proximal tibia was commonly recognized as a risk for SSI among orthopedic oncologists [7], which was reconfirmed in this study. We hypothesized that soft tissue was also critical for the tumors in the distal femur and focused on the resection volume of quadriceps muscles. Its results showed that an elevated num-

Launch	Study code	Representative institution	Design	Status	Publications
2005	JOA project	JSSBJI	Retrospective multicenter	Finalized	[2,3]
2008	Study of SSI at five referral hospitals	Kyorin University	Retrospective multicenter	Finalized	[6]
2009	JMOG022	JMOG	Retrospective multicenter	Finalized	[8,9]
2019	Analysis of the BSTT registry	Kyorin University and NCC	Retrospective registry analysis	Finalized	[10]
2021	J-DOS	JSSBJI	Prospective registry analysis	Ongoing	NA
2022	JMOG070	JMOG	Retrospective multicenter	Protocol processing	NA

Table 1. A list of nationwide surveys on SSI/PJI of tumor endoprosthesis in Japan.

Abbreviations: JOA, Japanese Orthopaedic Association; JSSBJI, Japanese Society for Study of Bone and Joint Infections; SSI, Surgical Site Infection; JMOG, Japanese Musculoskeletal Oncology Group; BSTT, The Bone and Soft Tissue Tumor; NCC, National Cancer Center; J-DOS, Japanese Database of Surgical Site Infection, NA; not applicable.

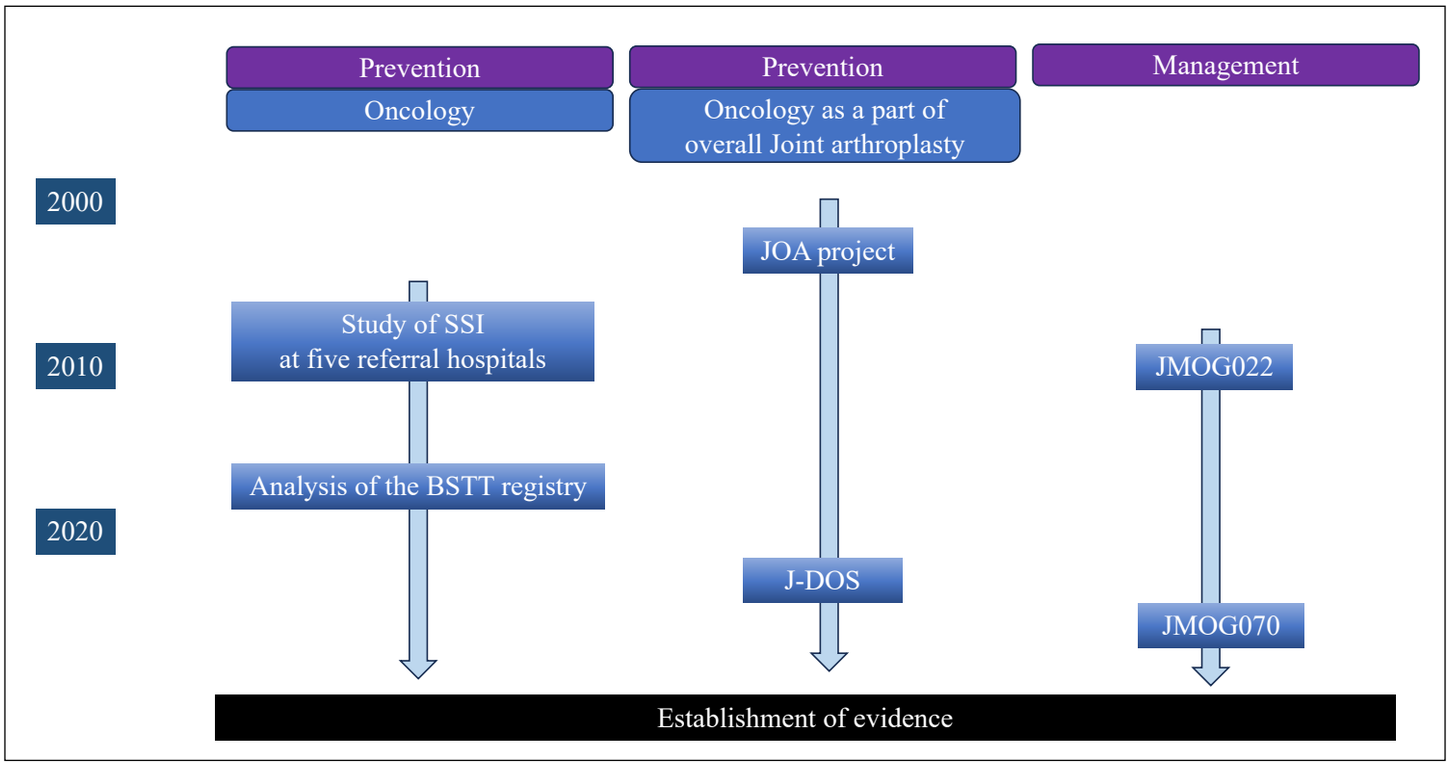

Figure 1. Progress in a nationwide survey on SSI/PJI in tumor endoprosthesis in Japan. Studies were classified according to their purpose: prevention and management. The incidence and risk factors of SSI/PJI are identified by accumulating and comparing cases with and without SSI/PJI. Precise decision-making can be achieved using data focused on the detailed clinical findings and treatment course of SSI/PJI.

Abbreviations: JOA, Japanese Orthopaedic Association; JMOG, Japanese Musculoskeletal Oncology Group; BSTT, Bone and Soft Tissue Tumor; J-DOS, Japanese Database of Surgical Site Infection.

ber of quadriceps resected for tumors was a risk factor for SSI. Prior surface infection and skin necrosis were also demonstrated to be risk factors for SSI.

3. JMOG022

Next, the first author and their colleagues focused on the treatment outcomes for SSI/PJI in tumor endoprosthesis and planned a nationwide retrospective multicenter study as Japanese Musculoskeletal Oncology Group (JMOG) members. JMOG was founded in 1981 to promote multicenter studies for musculoskeletal tumors, a representative of rare cancers. Today, the project involves 82 referral hospitals for musculoskeletal tumors and has supported more than 70 multicenter studies. This study is considered an initial multicenter study for SSI in tumor endoprosthesis in Japan [8,9]. Among the 388 registered cases, 57 (14.7%) were diagnosed with an SSI. The collected clinical findings include body temperature, C-reactive protein (CRP) level, white blood cell (WBC) count (Figure 3), culture results, the rate of successful infection control, treatment modalities (e.g., débridement, antibiotics, and implant retention [DAIR]), one- and two-stage revision, and risks of infection control failure and amputation. The successful infection control rate was 84.2%. Tibia location, intra-compartmental tumor location, and early infection presentation were associated with early successful infection control. The rate was significantly higher in the modalities with prosthesis removal than those with prosthesis preservation. Two-stage revision was the most promising modality for infection control. This study provided considerable data to the systemic review by the Musculoskeletal Tumor Working Group of the Second International Consensus Meeting for Musculoskeletal Infection held in Philadelphia in 2018 [1].

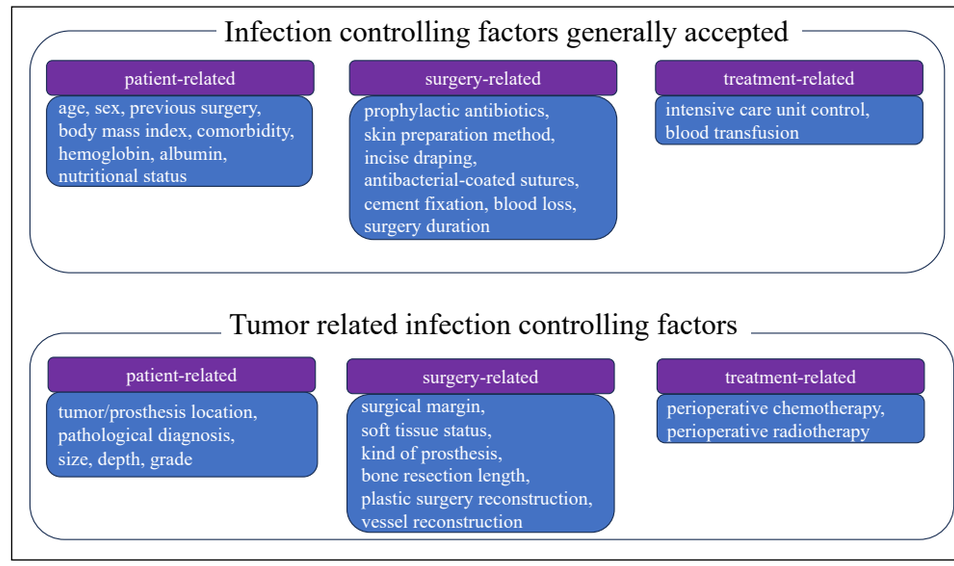

Figure 2. General and oncology-specific factors influencing SSI/PJI. In analyzing SSI/PJI in tumor endoprosthesis, both tumor-related factors and generally accepted risk factors for SSI/PJI in conventional arthroplasty should be considered.

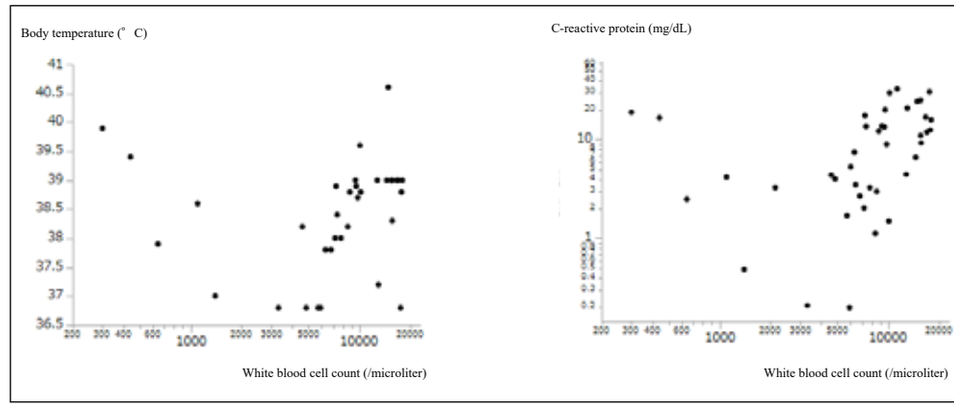

Figure 3. The relationship of WBC count with body temperature and CRP level at SSI/PJI diagnosis. SSI/PJI can occur during the myelosuppression period caused by postoperative chemotherapy. The five cases with a WBC count of <2000 /microliter indicate SSI/PJI during myelosuppression. In such cases, the WBC should not be considered a marker of SSI. In general, the WBC count was positively corrected with the CRP level and body temperature at SSI diagnosis. However, these factors were significantly negatively correlated with post-chemotherapy SSI/PJI. Therefore, the SSI diagnosis should be made cautiously during myelosuppression periods in tumor endoprosthesis and be based on body temperature and CRP level but not WBC count (unpublished data from JMOG022).

4.Analysis of the BSTT registry [10–12]

The Bone and Soft Tissue Tumor (BSTT) registry was launched by the JOA in Japan in the 1950s and promoted by the National Cancer Center (NCC). All JOA-certified hospitals for musculoskeletal oncology (N = 89) are obliged to participate in this registry [13,14]. The first author and their colleagues attempted to use the BSTT registry data to examine SSI/PJI in tumor endoprosthesis [10]. From 2006 to 2019, 18,975 cases of primary bone tumors were registered in the BSTT registry, of which 1342 were diagnosed as primary malignant bone tumors with prosthesis reconstruction. The primary endpoint was SSI/PJI, which was defined as "*cases that needed surgical intervention for SSI control* [10]." SSI was detected in 110 cases (8.2%) in this cohort. Multivariate logistic regression identified pelvis and proximal tibia location, tumor grade, an indication for myocutaneous flaps, and delayed wound healing as independent risk factors for SSI. Multivariate analysis is impossible without such a large sample size. The structure of the registry initially focused on clinicopathological issues of tumors rather than complications, such as SSI. Therefore, many variables reportedly important for SSI/PJI control were not collected, such as patient-related factors (body mass index, comorbidity, hemoglobin level, and albumin level), surgery-related factors (application of cement fixation, blood loss, and surgery duration), and treatment-related factors (intensive care unit control and

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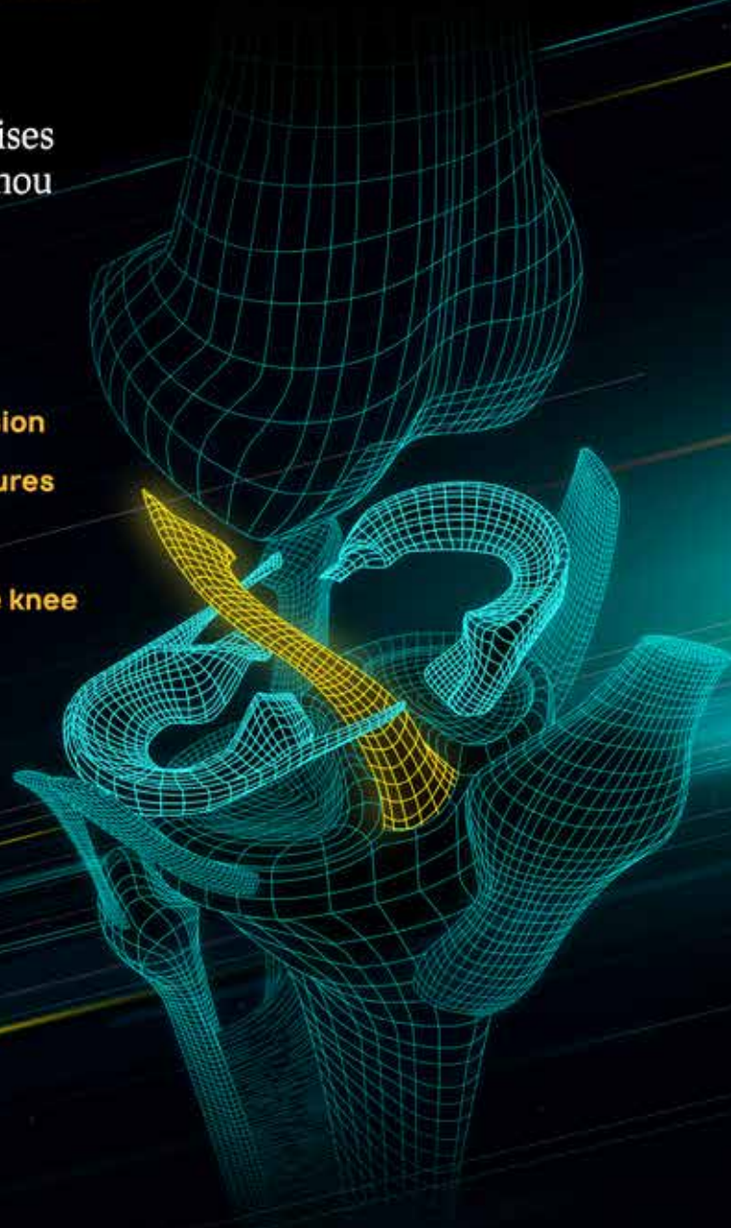

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Simultaneous translation

blood transfusion; Figure 2). The BSTT registry data has been used to examine infections in malignant soft tissue tumor resections and surgeries for bone and soft tissue sarcoma with biological reconstruction [11,12].

5. J-DOS

The major limitation of the initial JOA Project (see Section 2.1) was the unavoidable properties of a retrospective study. It is difficult to confirm whether all cases were registered during the study period without exception. Missing values cannot be entirely avoided. In addition, infection trends could not be continuously monitored over a long period. Therefore, a nationwide prospective survey called Japanese Database of SSI (J-DOS) was planned by the executive committee of the JSSBJI in 2015. Its primary endpoints, subjects, and inclusion criteria were almost identical to the initial JOA Project. Importantly, this study was designed to be prospective, with cases recorded via a web-based registration system. Every co-researcher participating in case registration was required to attend an e-learning session to understand the security, ethics, and structure of the registration system, ensuring the accuracy and safety of the study. The registration system has automatic warnings for missing values and logic errors. The prospective design ensures the recording of all cases during the study period. A continuous survey can be performed over a long time if needed. Hence several shortcomings of the 2006 project study could be overcome. The system was launched in 2021, and this study was adopted into the academic project research of the JOA in 2024. While the number of registered cases of tumor prosthesis reconstruction seems limited, the authors promote this system to JMOG-certified hospitals in Japan to accumulate tumor endoprosthesis cases.

6. JMOG070

In order to establish the principle for decision- making in management of SSI/PJI in tumor endoprosthesis, nationwide survey is now being planned in JMOG. While the inclusion criteria are similar to that in JMOG022 [8], this study is more focused on the treatment algorism of application of DAIR, one- and two-stage revision on SSI/PJI. SSI/PJI status, including the diagnosis period, culture results, body temperature, joint fluid, fistula, CRP level, erythrocyte sedimentation rate (ESR), and D-dimer level, as well as intraoperative findings such as loosening, will be collected under the hypothesis that the clinical findings of SSI/PJI could regulate the success rate of each intervention modality. The application principle is expected to be established by extracting the risk factors for SSI/PJI control failure.

DISCUSSION

This short review has described the history and perspectives of a nationwide study on SSI/PJI in tumor endoprosthesis in Japan. The advantages and disadvantages of each method should be considered cautiously when interpreting results (Figure 4). While the sample size of the multicenter study might be smaller, it enables the collection of data in specific settings and according to criteria strictly defined for the study purpose, ensuring quality control. For example, detailed patient symptoms, body temperature, blood test results, joint fluid condition, and comorbidities such as diabetes can be accessed more easily in such studies than in other study types [6,8,9]. As indicated in this review, there remains no ideal registration system covering both tumor-related and infection-related factors (Figure 2). Therefore, a prospective complication registration system for tumor endoprosthesis is urgently needed. The authors hope this review will help readers understand SSI/PJI in tumor endoprosthesis and thereby improve treatment outcomes. ■

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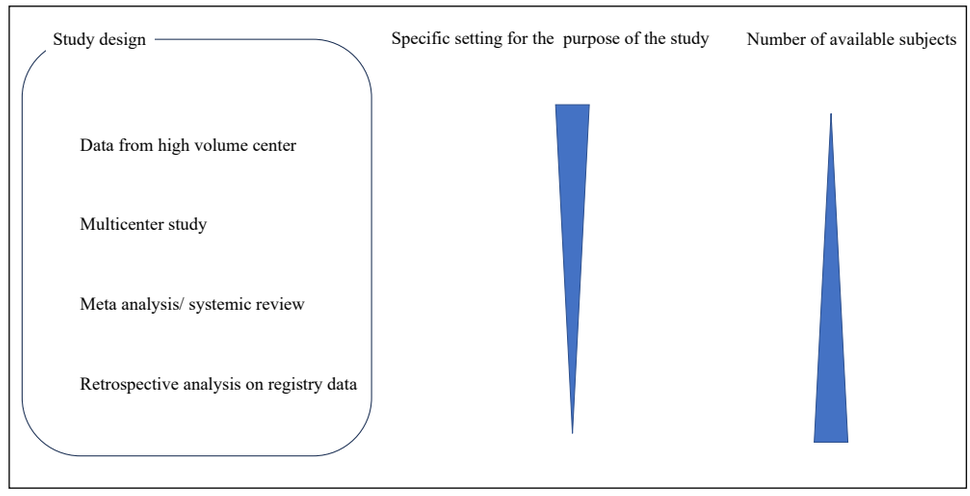

Figure 4. Properties of large-scale etiological studies. There appears to be a trade-off between the specific setting for the study and the cumulative number of available cases.

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