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SEPTEMBER, 01-02, 2022
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INTERVIEW

Hernàn J. del Sel

Hernàn del Sel is the current president of WAIOT and worked as a Professor of Orthopedics at the Catholic University until his retirement and is currently the Chief Medical Officer at the British Hospital in Buenos Aires, Argentina. He looks back to a very successful and fascinating career in Orthopedcis. He shares with us some very interesting stories on giants in Orthopedics he was able to meet during his training in Europe and the US. His father and these teachers had a strong influence on his career and the development of Orthopedics in Argentina.

: Professor del Sel, you are the current president of WAIOT. Can you explain what WAIOT is?

H.D.S.: WAIOT stands for World Association Against Infection in Orthopaedics and Trauma. It's an international society that gathers about 2000 members in about 100 countries. As the name says, it is focused only on infections in the locomotive apparatus. Most associations that we know so far, collect information from well-developed countries only. Although this is very valuable information, we at WAIOT believe sometimes it is slightly biased, because you don't get the deep information from less developed countries. We believe this is one of the strengths of WAIOT, since we have scientific input from all over the world: Middle East, Africa, the Indian subcontinent, Latin America and so on. WAIOT is an electronic society mostly. It has a free membership to whoever joins us through the internet and where you get most of the information that would be published or presented by our members.

: The first WAIOT congress in 2021 unfortunately was possible online only, but the second congress will be September 1st and 2nd this year in Cairo. What are the topics, and which people should join that congress?

H.D.S.: We had our first WAIOT congress last year. It was originally planned as a live congress in Greece, but then we had to go virtual since the pandemic went on. But this year we are having our second world congress and it will be the first one live. It will be mixed face to face and online, because there will still be some presentations in remote mode. Cairo in Egypt is a quite interesting location because in a way it is a sort of crossroads of civilisation. We are close to Europe with the European knowledge, and we are also in the north of Africa which has a lot to say about some infections that we don't usually see in Europe. The topics cover most of the infections of the musculoskeletal system, and there are some topics that are not usually seen in other meetings. For example tuberculosis, which is still prevalent in some countries. We go in a way from A to Z, and we will be covering not only infections in prosthetics, in implants, but there is a large experience in acute and chronic osteomyelitis. There

OVERVIEW

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The World Association against Infection in Orthopaedics and Trauma (W.A.I.O.T.): A Different Approach to Scientific Association.

WAIOT is currently the first and the largest scientific association focused on research, prevention and management of Musculo-Skeletal infection (MSI) and on biofilm- and implant-related infections in Orthopaedics and Trauma. Founded only five years ago in Vienna, in May 2017, WAIOT now counts more than 2,200 members from more than 100 Countries and growing. Since its conception, WAIOT was designed as 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.

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 fact, as recently reported in a WAIOT shared paper [1], bone and joint infections represent a tremendous "silent epidemic", causing every year millions of deaths and disabilities throughout the world. In order to accomplish its mission, WAIOT, is keen on bringing international experts together in an annual meeting to conduct a very rich scientific programme that updates orthopaedic-trauma stake-holders with the most recent researches and approaches in matter of prevention, diagnosis and management of musculoskeletal infections.
This year the **2nd WAIOT Congress** will be held on **September 1-2, 2022 in Grand Nile Tower Hotel, Cairo, Egypt,** hosted by **Prof Mohamed Fadel**, Congress Chairman and WAIOT Director for Africa. Congress Honorary Presidents will be **Prof Hernàn J. del Sel**, from Buenos Aires, Argentina, WAIOT President, and **Prof. Thami Benzakour**, from Casablanca, Morocco, immediate WAIOT Past-President (Fig. 1).

Figure 1: WAIOT 2nd World Congress in September 1-2, 2022 in Cairo, Egypt

The program will focus on **Osteomyelitis in the Pediatric and Adult age, Tuberculosis, Rare and Viral Bone Infections, Fracture-Related and Post-Traumatic Bone and Joint Infections, Bone Defects and Non-Union Management, Peri-Prosthetic Joint Infection Prevention and Management**.

In matter of **Spine Infections**, there will be a long and extremely full **Symposium**, in partnership with **AO Spine**. Moreover, another outstanding **Symposium on Orthoplastic and Diabetic Foot Management** is scheduled, organized in cooperation with the **Limb Reconstruction Society (LRS)** and, last but not least, a further special **Symposium** will be held together with the **World Orthopedic Concern (WOC) association.** All along the Congress, WAIOT recommendations and golden rules on management the musculoskeletal infections will be provided by experts from all over the world.
WAIOT is also cooperating with several existing institutions and scientific societies, including AAOT, AAOS, DKOU, LRS, AROM, IAC, EOA, ORTHOCON, TRAUMACON, SMACOT, etc..... In particular, WAIOT has participated with very well attended Symposia at all SICOT Orthopaedic World Congresses every year since its foundation and this year it will be also present in Kuala Lumpur, Malaysia, at the 42nd SICOT Orthopaedic World Congress.

Concerning editorial activities, since many years WAIOT has been working on articles and editorials on ortho-trauma infections, published in several journals [2, 3, 4]. In line with these efforts, a fruitful cooperation is now starting with **MO [My Orthopedics] Journal**. MO Journal has been publishing since more than two decades scientific articles, interviews and proceedings for orthopaedic surgeons and traumatologists, while its website features filmed presentations and debates from orthopaedic congresses, webinars, films of surgical techniques, and more. Characterized by a direct and practical approach, with several open access contents, MO Journal appears a logical and natural platform for WAIOT editorial activities, to further expand news and scientific knowledge worldwide in the field of bone and joint infection management.

Looking forward to seeing you all in the Beautiful City of the Nile and inviting you to join the WAIOT community at https://www.waiot.world, we wish you a good lecture of this special issue !
With warmest regards,

The W.A.I.O.T. 2022 Executive Committee

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is also a very nice presentation on open fractures and different treatments for open fractures. Mainly in low-resource countries in which they largely used Ilizarov methods with very excellent results. We all know that Ilizarov frame is a great method but sometimes is left aside for some other reasons. There will be also a spine symposium with infections of the spine. It is not too common to find a full whole symposium on spine infections, which is a very interesting topic.

: What do you see for the future of WAIOT?

H.D.S.: The future of WAIOT very much depends on what WAIOT does in the present. What we have to do, like anybody, is do a good job. If you do a good job, you will be rewarded for it. If you don't do a good job, you will probably disappear sooner or later. We are very proud that WAIOT has grown from 200-300 members five years ago, but about 2000 nowadays and we are still growing. Our success has probably only one clue, which is hard work and open arms. Open arms mean an open door to the entrance to WAIOT, to be able to share your experience regardless of where you come from. So, I believe the future of WAIOT is holding on to what we are doing today. Which is having this open policy. Of course, there is a selection committee for papers, but regarding the possibly of giving your opinion, WAIOT is a very open society.

: How do you cooperate with these existing infections societies, and what do you think is the advantage of WAIOT compared to the European or American infection society, for example?

The cooperation has mainly been within SICOT so far, which is the international orthopaedic society. Some of the European members of WAIOT are members of the European Bone and Joint Infection Society. We lag behind in adherence from the infectious and orthopaedic specialists in North America and Canada. However, I don't think there is anything better or worse between the societies. It very much depends on your scope or your area of influence. This is what I see, not better or worse but different. In WAIOT we have the open-door policy of having input from France, Egypt, Saudi Arabia, India from Brazil and many other countries. You get to listen to the bells ringing from different areas of the world.

: Let's come to your personal career. Where did you do your training?

H.D.S.: I graduated in 1972 in Argentina and I don't know if I have to be proud, but this August I will be celebrating 50 years as a doctor in Argentina. I come from a family of doctors. My grandfather was a GP, a well-known clinician in Buenos Aires, and my father, who would be 110 years old today, he was one of the professors of orthopaedics in Argentina. Argentina had a very strong European influence regarding its school of orthopaedics. For the best part of the 20th century, we had a very strong British, Italian and German influence. Not so much an American influence, which only came in the last part of the 20th century. I've been working in orthopaedics since I graduated. As I said, my father was a professor of orthopaedics in those days. But for some juvenile rebel impulse, I decided, at least in the first few years of my career, not to work under my father. So, I pursued a postgraduate career overseas, not in Argentina. My father had personal experiences as well in Europe. So I said, I'm going to the US to see what a residence would be like there. Of course, knowing that the residence would be a very fruitful one.

: You did your residency in 1974 to 1977 in Ohio. Please explain why you chose Ohio and why you left the umbrella of your father?

H.D.S.: I had some informal orthopaedic education from my father before graduating, but right after I graduated, I had a very good relation with my father, and in a way he encouraged me to have some training overseas, because at my return I could always give input to the Argentine society regarding training overseas, which was not so common in the early 70s. In those days, you had to apply for America with an exam which was called the Educational Council for Medical Graduates, which was a very hard examination. Then once you were there, you had to apply to whichever institutions you could. Those were quite heavily disputed spots, so you could not always choose the number 1 places like HSS in New York or Mayo Clinic in Rochester. I was accepted at Medical College of Ohio what was in those days a sort of new university, which had hospitals in different cities. I worked mostly in a mid-size town which is called Toledo in Ohio. However, with all the technical possibilities that the US gives you, working in a medium size city is the same as working in a large city. It was a very great and nice experience. After doing my orthopaedic residency in the US, and being in contact with my father, I said that I would like to pursue a career in some subspecialty. Mostly in those days I was thinking about hips and my father got in contact with Sir John Charnley. The story is quite nice, because my father had been a roommate of John Charnley right after the war in the UK, as a scholar of the British council. They had been good friends, even before John Charnley went on to be Sir John Charnley. So, he wrote to John Charnley, and John Charnley said, well I don't need to ask many more questions because he's your son, and if he's been trained in America, we don't even have to worry if he speaks English. I was accepted at the well-known Wrightington Hospital, and that was for 1 year. They don't call it a residency in the UK, they call it a registrar. So I went during 1978 as a senior registrar at the Centre for Hip Surgery in Wrightington Hospital. John Charnley was close to retiring then, and as you know, that was the mecca for hip surgery in those days. We had visitors from all over the world, every single week, with their noses close to the laminar flow enclosure. So that was a fantastic experience because we got to interchange opinions and knowledge with people from all over the world.

: Then you finally returned to Argentina, and how did you career proceed then?

H.D.S.: I would also like to add that I was fortunate enough during my career to be able to meet some other giants of orthopaedics. I had the pleasure of meeting Professor Ortolani in Ferrara, Italy and he was extremely kind to me, giving me his knowledge. I was a young surgeon, and I was like "wow" being with Professor Ortolani face to face. And there was a very nice professor in Gothenburg, Sweden, called Bertil Stener. And he worked alongside Alf Nachemson who was one of the great scoliosis surgeons of those days turning around the science. Working in the USA, I met Ray Gustilo, the open fractures titan. In those days, orthopaedics was at a turning point regarding technology and knowledge. I had the pleasure and the honour to be able to live along them. After my training upon returning to Argentina, my father was in those days working at the main university hospital. I went on to work at what was the Spanish Hospital, which was a hospital associated

with the university and whose chief was one of my father's initial pupils. Dr Scaramuzza, a very nice surgeon who was very nice to me. He said, come on, work with me, I would like to have a Del Sel; I had a Del Sel as a teacher, and I would like a Del Sal as a junior. So I went on and joined Dr Scaramuzza at the Spanish Hospital which is where I started to develop my career in Argentina in hip and knee surgery.

I had a complete orthopaedic training residency and coming back from the UK I was at the start of my career as a hip and knee surgeon. The first 8-10 years of my career in Argentina, I did most of the specialties, not only orthopaedics but also trauma. I was never very keen on hand surgery, which in those days had already been one of the first subspecialties to be defined together with spine surgery. Mostly I did limb surgery, both upper limb and lower limb trauma. But leaning towards hip and knee implants quite early in my career. However, I continued doing general orthopaedics until about the early 90s, when I started giving up ankle fractures, elbow fractures and so on, and dedicated mostly and specifically to hips and knees.

MO: When did you subspecialise in infection? Or was it just by being a hip and knee surgeon that you had to deal with infection?

H.D.S.: That is a good question. I returned from my training in the UK at Wrightington, which as you know was a centre for hip surgery. But even in those days, in the late 70s, we were doing a fair amount, about 20% knee surgery. And although the centre for hip surgery was focused on the prevention of infection by operating in laminar flow enclosures, we did get in those days already the severe complications of infections. Not only from those that occurred at Wrightington, but those coming from elsewhere in the UK. In a way, developing a 'taste' or a 'like' for infection when you do implants is a must, because infection is a complication that you will be facing, and you will have to be trained in it sooner or later. The knowledge and treatment of infection is very much dependent on your understanding of the infectious process. You will never heal it if you don't understand how it works and how the infection changes the metabolism of the bone and the bone turnover, which is the worst aggression that infection does on bone. So in a way, the liking of infection is something that I would say every hip and knee implant surgeon should know. Although the best of all worlds is having specialist centres for muscoloskeletal infections, at which of course the knowledge of implant infection will be paramount.

MO: Now let's move to your academic career. What was the topic of your PhD or your professorship? Was it already arthroplasty or what was the topic?

H.D.S.: That's interesting because my doctorship was on a specific area, which was osteonecrosis of the knee. You probably remember that osteonecrosis of the knee was an unknown entity until I think it was the last 70s or early 80s in which Bauer from Sweden described the individual osteonecrosis of the knee - remembering that osteonecrosis of the hip had been described only about a decade before. Osteonecrosis of the knee: I remember I spoke to my father about it and he said he didn't know what it is. Because most osteonecrosis went on to develop into full blown medial degenerative arthritis. But when you looked back at the patient's records and x-rays, it was not primary osteoarthritis but osteonecrosis. So that was my field of interest in those days and the title of my thesis was the not so well-known issue of osteonecrosis of the knee, which gave the way to my academic career. After that, I pursued my academic career at the New University of Buenos Aires and I ended up being the professor of orthopaedics at the Catholic University in Buenos Aires in Argentina, which is a private university sponsored by the catholic church.

MO: How developed was the scientific community in Argentina when you started your career?

H.D.S.: Argentina has had quite a strong scientific influence in most of Latin America for many years. Perhaps for the past 20–25 years, Brazil has grown and developed very much. But Argentina for the best part of the middle of the 20th century was the scientific place to come for knowledge in medicine and many other areas. My scientific career started in the early 80s, after I came back to Argentina in 1978. I studied my academic career alongside being an assistant surgeon, and my academic career was mostly at the University of Buenos Aires. Our links to the Catholic university came from the fact that the Catholic university has a British hospital as it's university hospital. So all the medical students from the catholic university do their pre-grad hospital work at the British Hospital in Buenos Aires.

MO: Currently you work at the British Hospital, but you are a member of the catholic university.

H.D.S.: I started my career at the Spanish Hospital in Argentina. As you know the Spanish community is very strong in Argentina, and the Italian as well. In Buenos Aires there is a Spanish, Italian French, German and a British hospital which are very well known. There is also a Jewish hospital, because they were tending to the large immigration community in those days. Funnily enough, I started my career at the Spanish Hospital, and I worked there for about 20 years. In 1997, I was appointed chief of the department of orthopaedics at the British Hospital, so I moved from one community to the other and I was the chief of orthopaedics at the British Hospital from 1997 to 2020. When I turned 70, I retired from my post as chief of orthopaedics and I'm presently the Chief Medical Officer at the British Hospital. My heart is always sitting at my desk in orthopaedics, so I still work as an orthopaedic surgeon, mostly.

MO: With this position you always had scientific contact with the British?

H.D.S.: Yes I always kept a strong scientific link with the UK. The Argentine school originally had strong links with Europe: UK, France, Germany, Austria as well, the Böhler school is very well known by all of us. I have visited Georg Ender at the Unfallkrankenhaus in Vienna because we were very keen on the Ender nails. So again, the connections between Argentina and Europe were very strong. Then the Americans began being strong in the second part of the 20th century, and most of us had some liaison with the Americans. Having been a pupil of John Charley it was not so hard to me to meet with John Insall, who was the father of total knee arthroplasty in the US. Having been able to personally meet John Insall and host him in Argentina was a very strong influence in our school regarding America. As I mentioned before, I also had the privilege to meet Ray Gustilo from Minneapolis, who was the father of classification of open fractures. Having the chance to be on the shoulder of giants gives you a much better scope, and a wonderful vi-

sion of the orthopaedic field. I feel privileged of having had that in my career and bring many of them personally to Argentina and lecturing with us in our yearly congress.

: Which of your teachers had the most influence on your career?

H.D.S.: That's a great question, because I had the privilege of having great teachers. There is a talk I am always asked to give at the national meetings which is exactly this: who had the most influence on my career? As I've said, but this is not my creation, we are always standing on the shoulder of giants. I always say my first giant is the one I had next door, which was my father. My father was one of the forefathers of infections. He had his very strict adherence and ideas on chronic osteomyelitis, which as we know is not a microbiological problem, it is a bone turnover problem. If you understand that you can cure it, if you give just antibiotics, you can never cure it. John Charley was one of my giants as well, as you can easily imagine. Because John Charley was not only a hip surgeon; he was an original thinker. The original thinkers blow up your mind when they start thinking. John Charley was somebody unbelievable to be with, because you could have lunch with him and ask him what he thought about, say, ankle fractures, and if he was in the mood he would give you an unbelievable lecture about ankle fractures, and if he was not in the mood, he would carry on talking about other things. He was an unbelievable genius. John Insall and Ray Gustilo also exerted an influence on me too.

: You were traveling a lot, building a scientific career and being head of several departments. How did you balance your private life with your family?

H.D.S.: This is probably the hardest question of all. Because when we start our careers, we want to do everything, because we are young and the whole road is ahead of us, and we want to travel the road as fast as possible and cover it all. I mean, we want to travel the road and get to know every place we travel to. We all know that having a strong and busy academic and assistance career in a way takes precious time from your personal life and from your family. We have all sacrificed time from our families. However, I did get married in 1980, and I have today two sons who are 38 and 35 years old. None of them pursued a medical career! One lives in Canada and he works on the environment, and my other son works in Argentina in the economy. The medical tradition, at least on my side coming from my grandfather and my father and myself, was cut. But I do have a brother who is an orthopaedic surgeon as well, so you can imagine the influence that my father exerted. And my brother has two sons who carry on the family name in orthopaedics. Regarding time, fortunately enough, I did have a very understanding wife and children. We went along many years and they allowed me to do my career and I did take care of them to the best of my ability. Then again, I have always been very keen on sports. When you come home at 7 or 8 in the evening and you're tired from working and having your brain working all day, I believe one of the best things you can do is something for your body. You can either go swimming or play tennis or ride a bicycle. I personally have a very strong affinity with horses and like to play polo. In Europe, it sounds like only the rich and the royals do it, but in Argentina it's not expensive at all. What is kept for the royals and millionaires in Europe and US, we do it in Argentina. It's very nice having a communion between the horse, which is a wonderful noble animal, and the human being. It's a very nice sport. Kind of dangerous as well, but it's nice!

: If a young surgeon approaches you now and asks, what do I need to be as famous and good surgeon as you? What do you recommend?

H.D.S.: That's a good question. Good question are ones you know the answers. The interesting thing is what you're asking me has fortunately been put to me many years ago already from the people that trained with us or asked advice for what they have to do in their careers. Our school of orthopaedics has widespread pupils all over the country and Latin America. The answer is, it's not easy to accomplish but it's easy to answer. To be successful, you have to be honest, you have to work hard, and you have to do that every single day. Be honest and work hard. And the results will come, sooner or later. But honesty is not easy – you have to be very cruelly honest with yourself. You have to learn from what you do well, and mostly you have to learn twice as much from your mistakes. When you have poor judgement. you always can say you can have poor judgment by not knowing, and you can have poor judgement by asking someone who doesn't know. So choosing your counsellors, your masters and your giants is what you have to do, to emulate what others have done before you. Be honest, work hard, and that's about it.

: Thank you very much Professor Del Sel for this nice interview.

NOVEL DIAGNOSTIC APPROACH TO BIOFILM-RELATED INFECTIONS USING DITHIOTREITOL (DTT)

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INTRODUCTION

The implants generally used to surgically treat or manage several patients may act as a biotic surfaces in the human body, thereby facilitating the colonization and the settle of many microbial species. Microbes are often cleared by the host's innate immune mechanisms, but sometimes they can cause a devastating life threatening infection, generally called Implant-associated Infection (IAI). The main reason of these infections is because bacteria adhered to the implant surfaces are less susceptible to killing/elimination by the immune system (1). In addition, these bacteria may survive on the implant surfaces and develop biofilms that reduce the effect of antimicrobial agents and result in a persistent colonization which confers them an “embedded biofilm status”, then consequently difficult to be dislodged and identified. In order to detect the true pathogens, disruption and demolition of the biofilms should indeed precede the standard microbiological methods (2).

Recently, Wildelman et al. reported that all-cause 10-year mortality is higher for patients with PJI (45%) compared with patients undergoing THA without PJI (29%). This can be due to the natural evolution of the implants, but also to the difficulty to manage these infections even microbiologically (3). As matter of fact, it is important to point out that inaccurate diagnosis should be worth of attention in order to avoid any misunderstanding in the laboratory setting as well as in the clinicians. False positive and negative results are very deleterious for the patients and frustrating for the surgeons.

Biofilm- and implant-related infections are constantly looking for definitive guidelines and resolutive diagnostic approaches, it is therefore necessary to pay the utmost attention when dealing with these topics, certainly controversial and to be further improved. This paper summarizes the main microbiological tools to improve diagnosis and avoid unreliable results.

MICROBIOLOGICAL DIAGNOSIS

According to the WAIOT Guidelines (4), the culture and isolation of the microorganisms is the main useful approach for the diagnosis of prosthetic and joints infections. Samples suitable for the microbiology Laboratories can be periprosthetic tissues, joint fluid and/or prosthetic components removed during the revision procedure. Swabs must be avoided and a minimum of 3-6 periprosthetic tissue samples and prosthetic components should be collected on the basis of clinical stage, the type of suspected infection (low-grade or high-grade) or microorganism (low or high virulence). Microbiological procedures, from the sample collection until the microbiological report, requires specific and mandatory conditions: a) to avoid samples contamination; b) to use closed and sterile transportation systems; c) certified laboratory processing methods to avoid false positives or false negatives results.

The pre-analytical phase and samples preparation is very relevant to perform a reliable diagnosis. So, the use of antibiofilm techniques for explanted biomaterials and for biopsies is definitively mandatory. The formation of biofilms is intrinsic to the pathogenesis of PJIs, so many diagnostic tools have been used but many biases remain still open so far. The pre-analytical phase is very important to increase bacterial retrieving after biofilm dislodgement.

PRE-ANALYTICAL TOOLS USED TO IMPROVE DIAGNOSIS

Authors have conducted several analyses of the various microbiological methods to diagnose implant-related infections, outlining the advantages and disadvantages of the various techniques today available. Today, the physical (Sonication) and the chemical treatment (Dithiothreitol at 0.1%) can be used to pre-treat samples and dislodge bacteria from their biofilm.

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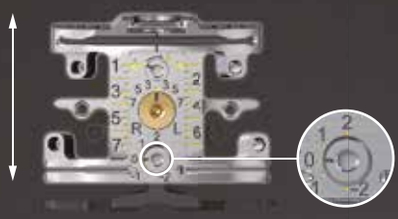

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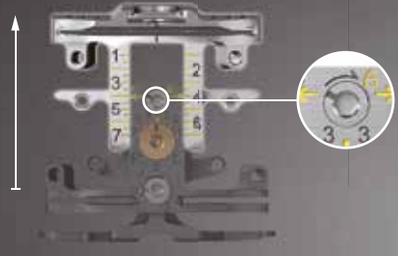

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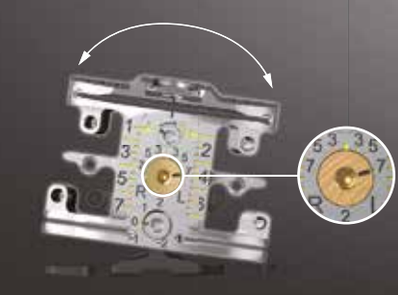

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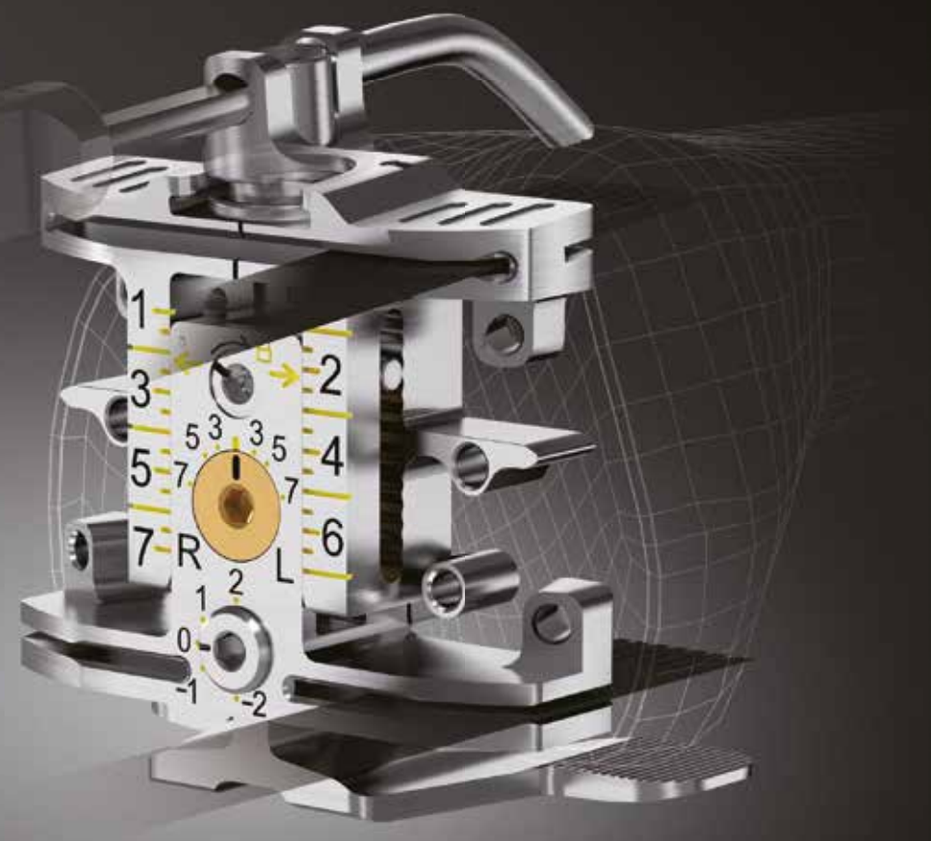

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Sonication

The containers with prosthetic components need to be handled under a laminar air flow cabinet and covered for at least 90% of its volume with Ringer's solution or sterile physiological solution. The samples are vortexed for 30 seconds, sonicated at 30-40 KHz 0.22 ± 0.04 W / cm2 for 5 minutes and vortexed again for additional 30 seconds. All these procedures must be performed with attention in order to minimize possible contamination (5).

Dithiothreitol (DTT)

An alternative to the sonication is the use of a solution of dithiothreitol (DTT), which reduce the disulphide bounds in biofilm, providing a chemical debonding [68]. In this case a sterile solution of 0.1% (w: v) of dithiothreitol (DTT, formula C4H10O2S2, molecular weight: 154.2) in phosphate buffer saline (PBS) will add to cover the prosthetic components. The container with prosthetic components and DTT solution will be shaken up at about 80 rpm for 15 min (6,7).

Comparison between the two methods

The literature on sonication has demonstrated satisfactory results especially in the setting of a non-suspected PJI and proven of superior diagnostic capacity over traditional cultures. However, the aforementioned method has some drawbacks, especially the high cost of equipment to many parts of the world and cross-contamination risks. The introduction of chemically based biofilm breaking techniques (i.e., dithiothreitol) has been developed to avoid risk of contamination and improve diagnosis. A recent meta-analysis (8), collecting data from comparative studies with 726 implants, demonstrated that the diagnostic accuracy of DTT and sonication were 86.7% (95% CI 82.7 to 90.1) and 83.9% (95% CI 79.7 to 87.5), respectively. Pooled sensitivity and specificity showed no statistically significant differences between DTT and sonication, and that sonication is not superior that DTT.

NEW DTT TECHNOLOGY IN A STERILE AND CLOSED CIRCUIT

A completely closed circuit from the surgical field to the microbiological lab have been recently developed, which prevents sample contamination, thus increasing the specificity. MicroDTTect (Figure 1, kindly provided by NovaHealth srl, Italy) represents indeed the first and the only patented system for sample microbiological collection, transport and processing, that combines the increased sensitivity of the DTT with a completely closed system. This system could have the advantage to allow any lab and any clinic to maximize microbiological testing without the need for special training or expensive machines. It also has the advantage of processing simultaneously or separately multiple samples, including tissue samples, fluids, implants and biomaterials. Figure 2 describes the necessary steps to be followed from the Operative Room to the Laboratory.

COST BENEFIT ANALYSIS OF ANTIBIOFILM METHODS

Cost-benefit analysis of antibiofilm microbiological techniques for peri-prosthetic joint infection diagnosis has been published (9). This analysis highlights the potential economic advantage to hospitals associated with the routine introduction of antibiofilm techniques for microbiological diagnosis of PJI. Authors considered an average of five samples per patient, processed separately with traditional tissue culture with or without sonication of prosthetic components, or pooled together using the MicroDTTect device. They calculated that the overall mean direct cost per patient was € 397 and € 393 for sonication or MicroDTTect, respectively, compared to € 308 for traditional tissue cultures. In terms of opportunity costs, MicroDTTect was the most effective technique, allowing for a 35% or 55% reduction in time required for sample treatment, compared to tissue cultures combined or not with sonication, respectively. Pooling together direct and

Figure 1: MicroDTTect system

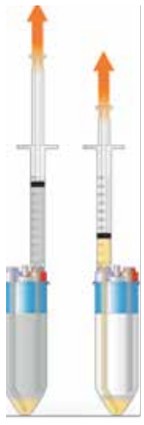
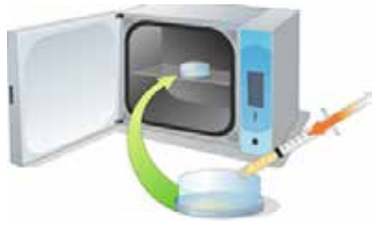
Steps from MicroDTTect Procedure		
1	**2**	**3**
Place the explanted sample inside the device 	Remove inside air, close the device hermetically 	Snap of the red valve to connect the two chambers 
4	**5**	**6**
Place the device on the mechanical shaker for 15' (80 rpm) 	Snap of the stem of the blue valve 	Withdraw the elute through the syringe 
7	**8**	**9**
Centrifuge the test tubes 	Remove the supernatant form red access and the pellet form blue access 	Perform microbiological culture in accordance with laboratory protocol 

Figure 2: MicroDTTect procedure

indirect costs associated with false positive and negative results of the different diagnostic techniques or unnecessary medical treatments and possible medical claims, MicroDTTect or sonication become increasingly cost-effective when the extra-costs, generated by diagnostic inaccuracy of traditional tissue culture, took place, respectively, in 2% or 20% or more of the patients.

DISCUSSION

One of the main challenges of Implant Associated Infections (IAIs) comes from the striking ability of bacteria to adhere to the inert surfaces, forming biofilms which make the microorganisms much less susceptible to killing/elimination by the immune system. Bacteria embedded in biofilms are also difficult to be dislodged and identified by traditional microbiological techniques. In order to detect the true pathogens, disruption and demolition of the biofilms has then been proposed by different means in literature.

Procedures for samples pre-treatment in order to dislodge bacteria, such as sonication of retrieved implants, is better than conventional cultures for the diagnosis of device-related infections. However, the significance of some isolates in patients without clinical infection remains uncertain, and the risk of false positive as well as false negative is still high and need to be further defined. The over antibiotics treatment can be counterproductive when a contamination occurs and the true pathogens are not isolated. This is why research on the field is still looking for alternative methods that are less laborious and with streamlined and fast algorithm from the surgery room (where the sample are collected) to the Laboratory (where the samples are processed).

A recent paper by Oliva A et al. (10) has performed an acute analysis of the various microbiological methods to diagnose implant-related infections, outlining the advantages and disadvantages of the various techniques today available. However, inside this paper some points that may have a great relevance for the daily clinical activity, need to be better clarified and discussed.

Drago et al. (11) have recently underlined that "Dithiothreitol Assay" should be considered a "Culture based" methods, as the sonication one.

Both methods are indeed "culture-based", since they both aim at dislodging bacteria from a given sample (DTT by chemical means, sonication by physical action), with the resulting processed fluid from both procedures requiring further culture to identify the pathogen(s).

No substantial difference there are indeed between sonication and Dithiothreitol as to regard the need for microbiological examination and concerning the possible choice of the microbiological technique used to identify the pathogen (traditional culture in many cases, or molecular or other methods in fews).

In fact, both antibiofilm processing methods often require a subsequent bacterial cultural examination, that can be chosen among all of those currently and routinely available in laboratories, as both sonication and Dithiothreitol only provide bacteria dislodgment from the biofilms prior to culture or the direct examination by molecular methods.

Dithiothreitol is effectively used since decades in the analysis of sputa for the diagnosis of broncho-pneumonia, and Streptococcus pneumoniae is well known among microbiologists as one of the most labile bacteria. So, the hypothesis that Dithiothreitol may have a toxic effect is clearly contradicted by the same literature that the Oliva et al. cite, including the large clinical trials performed by Sambri et al (7).

Even one of the most recent studies, performed on collection strains and not on clinical isolates, did show how planktonic bacteria viability after exposure to Dithiothreitol is exactly the same as that is found after exposure to sonication and even to NaCl 0.9% alone (12).

Randau et al (13), demonstrated that DTT was inferior in sensitivity when diagnosing PJIs compared to sonication fluid cultures and tissue biopsies, but only when pH in the DTT was low. When improperly used (unstable solution, very low pH, DTT-samples contact for a long time or days, higher concentrations), DTT fluids correlated indeed with false-negative results.

This is very similar to what can be found for sonication, that is known to have the ability to kill bacteria (14) and requires an accurate choice of the ultrasound parameters to avoid bacterial growth inhibition.

In addition, Randau et al (13), evidenced that sonication had better sensitivity but lower specificity. The Authors concluded that the closed system of the DTT kit avoids contamination and false-positive results, and that DTT can be an alternative where sonication is not available.

False positive results and samples contamination during collection, transportation and laboratory procedures remain challenging and not fully solved so far. Contamination is often overlooked in the surgery rooms during samples collection and in most laboratories during the processing or biofilm pretreatment.

All procedures which require standards of hygiene and proper and useful disposables or equipment when handling samples and special care is then required to be taken as per recommendations in microbiological testing laboratories.

In conclusion, we need to build specific procedures/guidelins and/or to apply dedicated devices for avoiding contaminations and any false positive results, as well as the negative ones. In this scenario the DTT device represents the first completely closed system to collect, transport and process retrieved biomaterials and tissues to diagnose implant- and biofilm-related infections.

CONCLUSION

Orthopaedic infections are common and devastating issues in the clinical setting. Prosthetic and orthopaedic infections are often neglected by the scientific community, but their incidence is increasing as well as the difficulty to treat these types of infections. Diagnostics tools are often not correctly applied, the antibiotic treatments fail to have success because the increase of bacteria resistance and the presence of biofilms is able to protect the pathogens. Infections, especially those iatrogenic and nosocomial, are receiving increasing attention and visibility because the high rate of legal litigations and the negative outcomes for the patients which impair their life's quality. A prompt and true diagnosis is essential at any level of suspicion of infection to avoid delay of medical or surgical treatments. For these reasons, infection prevention, the right and quick recognition of the infection, and the prompt attention by the healthcare personnel are of paramount importance. Accurate diagnosis remains difficult, as most signs of infection are subjective, so a multidisciplinary approaches and new tools are necessary to finally improve this challenging disease. ■

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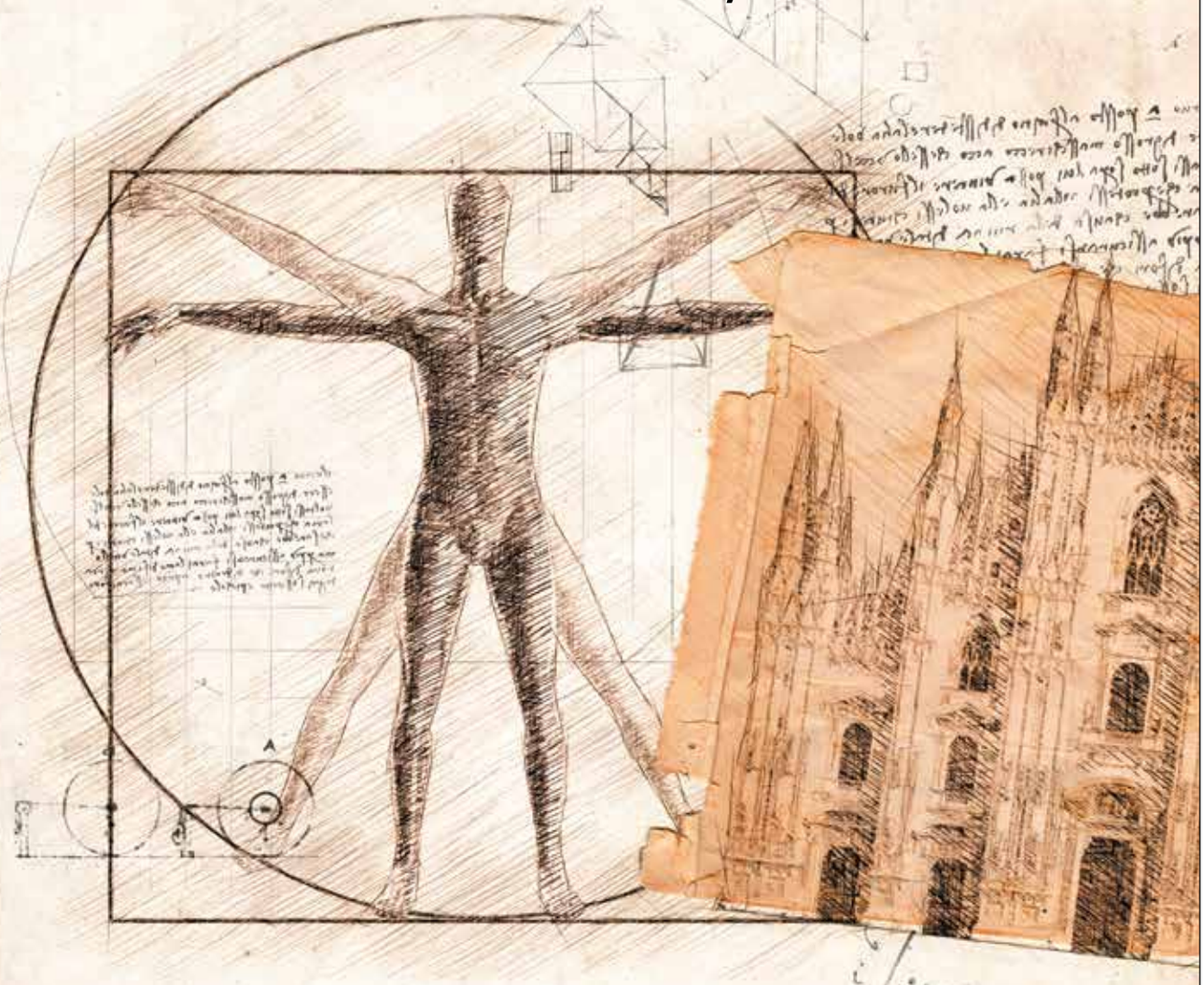

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ANTIBACTERIAL COATING OF IMPLANTS: WHAT SURGEONS SHOULD KNOW

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THE IMPACT OF BIOFILM- AND IMPLANT-RELATED INFECTIONS IN ORTHO-TRAUMA

Up to 80% of human bacterial infections are biofilm-related, according to the U.S. National Institutes of Health [1]. Among these, implant-related infections in orthopaedics and trauma still have a tremendous impact [2]. In fact, peri-prosthetic joint infection (PJI) is among the first reasons for joint replacement failure [3], posing challenging diagnostic and therapeutic dilemmas [4], with extremely high economic and social associated costs (Table 1). [5]

Leading reason for revision: Peri-prosthetic hip and knee infection is among the first three reasons for joint replacement failure, according to the registers; [6]
Infection risk after joint arthroplasty: the incidence of peri-prosthetic joint infection (PJI) **ranges from 1 to 2% after primary implant and up to 10% after revision surgery and in oncological reconstructions** [3].
Infection risk after osteosynthesis: the incidence of surgical site infection (SSI) after osteosynthesis for closed fractures of the long bones **range from 2% to 10%** [9]. The incidence of SSI after Gustilo 2 or 3 open fractures of the long bones is > 20% [10]
Mortality risk: the adjusted relative mortality risk (RR) for patients with hip revision for PJI, compared with the patients who did not undergo revision surgery is 2.18 [7]. The RR for patients undergoing hip revision for PJI, compared with aseptic hip revision range from 1.87 to 3.10; [8]
Additional costs: the average cost of management of infection after hip fracture surgery is **> 30,000 Euros** [8]. The cost of any single case of hip or knee PJI management ranges from **40,000 to > 100,000 Euros** [11, 12].

Table 1. Impact of implant-related infections in orthopedics and trauma: facts and figures.

PATHOGENESIS OF IMPLANT-RELATED INFECTIONS AND ANTIBACTERIAL COATING RATIONALE

Whenever a biomaterial is implanted, a competition starts between the host's and the bacterial cells for surface colonization. In the event of bacterial adhesion to an implant, immediate biofilm formation starts, making the bacteria extremely resistant to host's defense mechanisms and to antimicrobials[13]. In fact, in a wet environment, like the human body is, bacteria are capable to immediately adhere on a surface and to produce a protective intercellular matrix (the "biofilm"), which is completely formed in few hours. Once established, the biofilms efficiently protect the microorganisms both from the host's immune system and from the systemically administered antibiotics.

This immediate colonization of the implant from the bacteria can happen at time of surgery soon after the biomaterial is implanted in the body [14], even if the clinical consequences of the implant colonization may only become evident weeks, months or even years after the initial bacterial adhesion. The pathological consequences of the bacterial adhesion on an implanted biomaterial, generically termed as "post-surgical infection", features the presence of variable inflammatory signs and markers, pain and progressive implant loosening, whose timing and extent depends very much on the balance between bacterial behavior and the host's individual inflammatory response.

This observation, grounds the basis for providing all the implantable devices with a surface finishing or a coating, specifically designed to selectively prevent bacterial adhesion and biofilm formation at the very time of surgery, without interfering with the biocompatibility and the long-term duration and function of the implant [15]. Despite this urgent need, the development of antibacterial coating technologies for large scale use appears particularly challenging, due to the many requirements that they must fulfill [16]. In fact, while antibacterial coating of implants is advocated by many as a possible solution to reduce the burden of implant-related infection in orthopedics, remarkably few technologies are currently available in the market, with proven clinical safety and efficacy.

ANTIBACTERIAL COATING TECHNOLOGIES CLASSIFICATION

Various technologies have been investigated in the last decades and can be classified according to their mechanism of action in 3 groups (Table 2):

1. Passive surface finishing/modification (PSM)

This approach aims at preventing or reducing bacterial adhesion to implants through surface chemistry and/or physical modifications, without the use of any pharmacologically active substance. Examples of this approach include modified titanium dioxide surface or polymer coatings.

2. Active surface finishing/modification (ASM)

pharmacologically active pre-incorporated bactericidal agents, such as antibiotics, antiseptics, metal ions, or other organic and inorganic substances, are actively released from the implant to reduce bacterial adhesion. Examples of this approach are 'contact killing' active surface with silver- or iodine-coated joint implants.

3. Local carriers or coatings (LCC)

This strategy employs local antibacterial carriers, or coatings, that are not built into the device, but rather are applied during surgery, immediately prior to the insertion of the implant. They may have direct or synergistic antibacterial/antiadhesive activity or may deliver high local concentrations of loaded antibiotics or antibacterial agents [15].

Despite several products found effective at a research level, translating preclinical findings into clinical practice appears particularly challenging, time-consuming, and expensive. As a result, many promising coating technologies fail to reach the market due to regulatory, commercial or economic restrictions, denying the potential benefit to the patients and for the health care systems.

Features/examples	Development stage
Passive Surface/Finishing Modifications (PSM)	
Prevention of bacterial adhesion	
Hydrophilic surface	Preclinical
Superhydrophobic surface	Preclinical
Anti-adhesive polymers	Preclinical
Nanopatterned surface	Preclinical
Albumin	Preclinical
Hydrogels	Preclinical
Biosurfactants	Preclinical
Active Surface/Finishing Modifications (ASM)	
Inorganic	
Silver ions and nanoparticles	Market
Other metals (copper, zinc, titanium dioxide, etc.)	Preclinical
Non-metals: iodine	Clinical
Other non-metal ions (selenium, graphene, etc.)	Preclinical
Organic	
Coated/linked antibiotics	Market
Covalently linked antibiotics	Preclinical
Antimicrobial peptides	Preclinical
Cytokines	Preclinical
Enzymes and biofilm-disrupting agents	Preclinical
Chitosan derivatives	Preclinical
Synthetic	
Non-antibiotic antimicrobial compounds	Preclinical
'Smart' coatings	Preclinical
Combined Multilayer coating	Preclinical
Local Carriers or Coatings (LCC)	
Non-biodegradable	
Antibiotic-loaded poly(methyl methacrylate)	Market
Biodegradable	
Antibiotic-loaded bone grafts and substitutes	Market
Fast-resorbable hydrogel (acting both as passive surface modification system and as local antibiotic carrier)	Market

Table 2. Classification of antibacterial implant protection strategies. [15]

ANTIBACTERIAL COATING: CURRENT TECHNOLOGIES

Only few technologies are currently available in orthopedics and trauma for clinical use, or at least with reported clinical results (Table 3). These include silver and iodine coatings, antibiotic-loaded bone cement, gentamicin poly-l-lactic acid (PLLA) coating and a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and PLLA (Defensive Antibacterial Coating -DAC® Novagenit Srl, Mezzolombardo, Italy).

SILVER COATINGS

Different technologies are currently used to apply the silver coating to metallic orthopedic implants [17-19]. Comparative and prospective studies are not available and only retrospective case series have been published, with coating application restricted to tumor prostheses [20,21].
Wafa et al. [22] reported the results of silver-coated tumour prostheses in 85 patients compared with 85 matched control patients. Indications included 50 primary reconstructions (29.4%), 79 one-stage revisions (46.5%), and 41 two-stage revisions for infection (24.1%). At a minimum follow-up of 12 months, there was a significant reduction in the overall postoperative infection rate from 22.4% to 11.8% ($p = 0.03$) in favor of the silver-coated implant group, with a mean reduction of approximately 48% in infection rate.
The routine use of silver-coated implants remains rather limited for several reasons, including possible toxicity of silver ions [23], and selective coating, thereby providing incomplete protection of the implant, since the intramedullary part of the prosthesis and some modular components cannot be coated. Moreover, silver coating is currently available only for few implant designs and the high costs of this technology has resulted in limited use outside the oncology applications [24].

IODINE COATING

Povidone-iodine can be used as an electrolyte, resulting in the formation of an adhesive, porous anodic oxide with the antiseptic properties of iodine [25]. Besides extensive preclinical studies [25-27], excellent clinical efficacy was reported for iodine coating of titanium alloys in a continuous, non-comparative series of 222 patients [28]. Preoperative diagnoses included tumour in 95 cases (42.8%), 34 limb deformities (15.3%), 29 cases of degenerative disease (13.1%), 27 osteomyelitis (12.2%), 24 nonunions (10.8%), and 16 fractures (7.2%). A variety of implants were used: 82 spinal instrumentations, 55 plates for osteosynthesis, 36 external fixations (pins and wires), 32 tumour prostheses, ten hip prostheses, four knee prostheses, two nails, and one cannulated screw. At a mean follow-up of 18.4 months (3 to 44), acute infection developed in three tumour cases (1.9%).

Two more recent non-comparative studies – one investigating iodine coating and megaprosthesis [29], the other investigating total hip arthroplasty (THA) [30] – confirmed the safety and efficacy of the technology at longer follow-ups. Based on

Technology	Regulatory phase	Trademark and manufacture company	Mechanism of action	Main applications
Silver	Market	Agluna® (Accentus Medical Ltd, Didcot, United Kingdom); Mutars® (Implantcast GmbH, Buxtehude, Germany); PorAg (Waldemar Link GmbH & Co. KG, Hamburg, Germany)	Silver ion release	Tumour mega-prosthesis
Iodine	Clinical trials	Not applicable	Iodine release	Titanium implants including spine instrumentation, hip and knee joint arthroplasties, plates and screws
Gentamicin poly (D, L-lactide) matrix	Market	UTN PROtect Tibial Nail® (DePuy Synthes, Bettlach, Switzerland); Expert Tibial Nail (ETN) PROtect® (DePuy Synthes, Johnson & Johnson, New Brunswick, New Jersey)	Gentamicin release	Tibial nail for the treatment of tibial fractures and nonunions
Hyaluronic acid and poly (D, L-lactide) hydrogel	Market	Defensive Antibacterial Coating (DAC®) (Novagenit Srl, Mezzolombardo, Italy)	Antifouling activity with ancillary antibiotic release	Orthopaedics, traumatology, dentistry, and maxillofacial implants

Table 3. Comparison of clinically available antimicrobial coating technologies, specifically designed for orthopaedics and trauma implants

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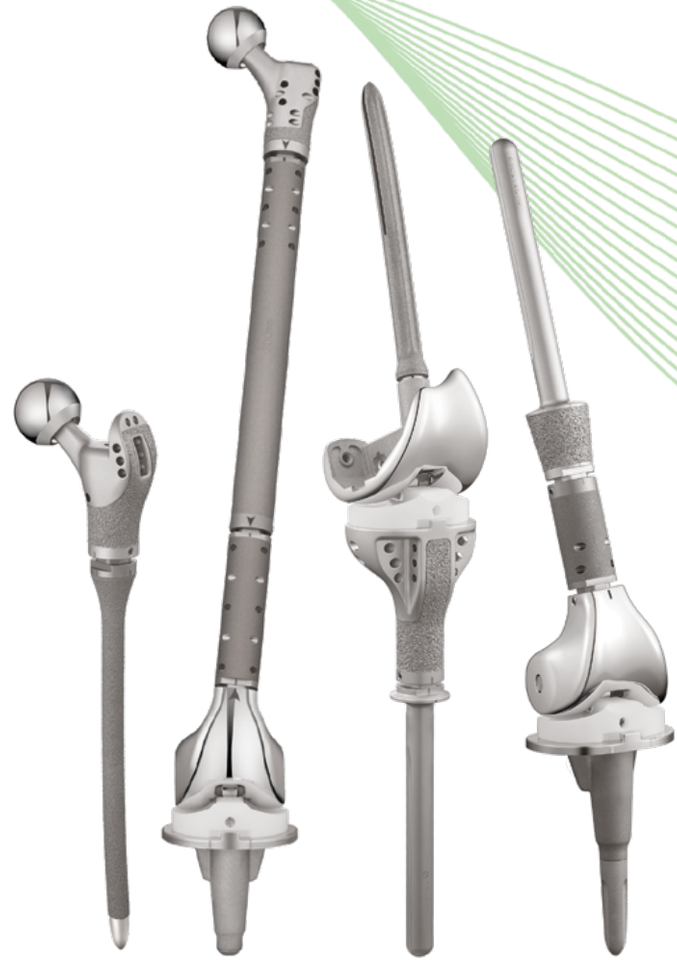

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these findings, clinical trials are currently ongoing to meet the regulatory requirements for market approval (Fig. 1). While no adverse event has been reported to date, the longer-term effects of local application of iodine coating and the application to materials other than titanium are yet to be assessed.

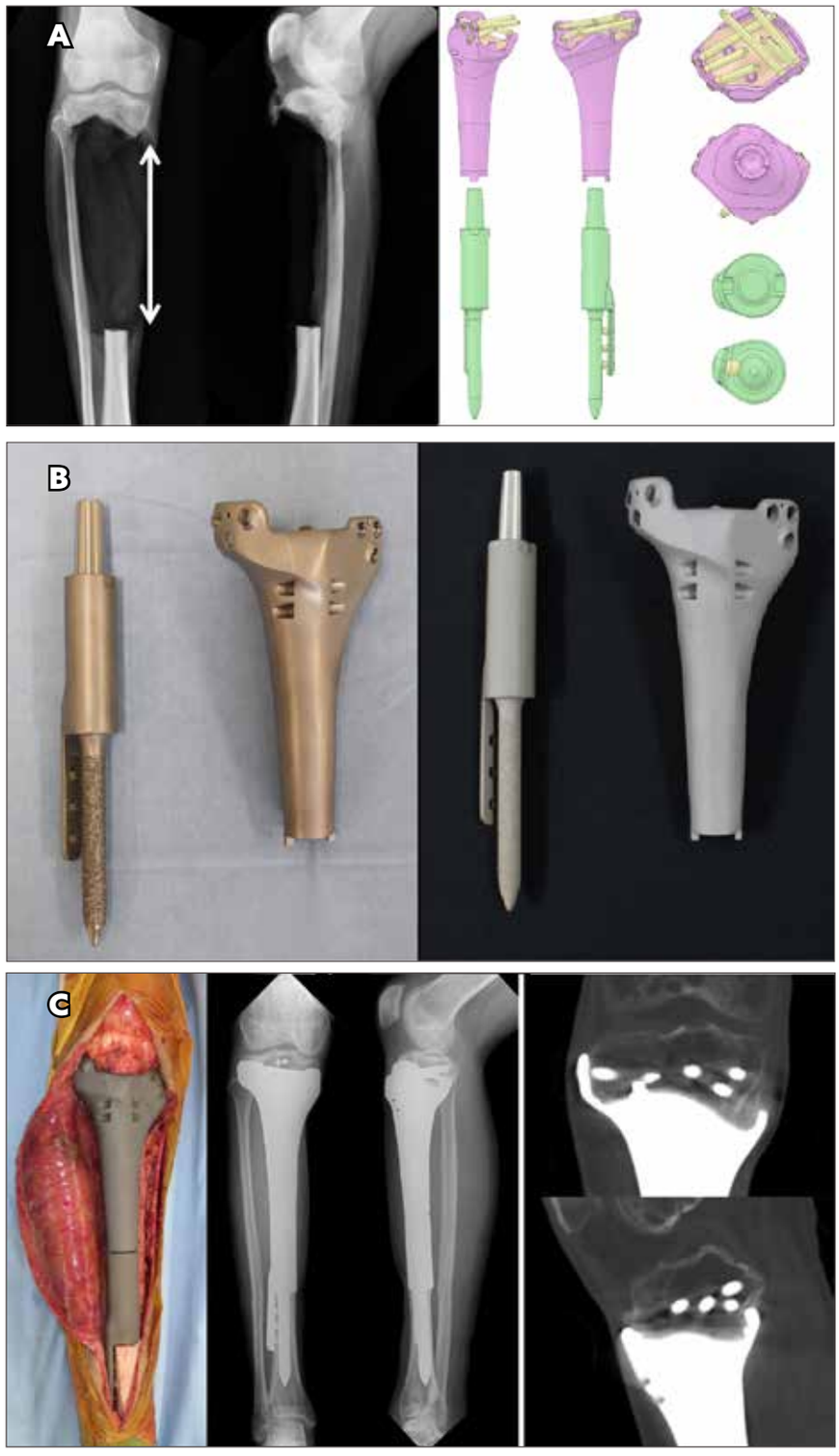

Figure 1 A to C. A. Left: 20 cm intercalary defect after tumor resection. Right: Custom-made implant with 3D printer. B. Left: Custom-made titanium implant with 3D printer. Right: The implant after surface modification with iodine (off-label). C. Left: intraoperative picture after reconstruction (off-label use), Center: Radiograph 1 year after operation. Right: Excellent bone ingrowth.

ANTIBIOTIC-LOADED POLY-METHYLMETHACRYLATE (PMMA) BONE CEMENT

Even if antibiotic-loaded bone cement was not originally designed to act as an antibacterial coating, it is currently widely used to mitigate the risk of septic complications after joint replacement with cemented implants. Moreover, antibiotic-loaded cement spacers are often employed to deliver local antimicrobials in two-stage revision procedures for peri-prosthetic infection [31]. The most common combination of antibiotics to be added to bone cement is aminoglycosides (gentamicin or tobramycin) with vancomycin. The most recent systematic reviews and meta-analysis confirm the efficacy of antibiotic-loaded bone cement to reduce the risk of post-operative infection after primary total joint replacement by a factor ranging from 20 to 84% [32, 33].

Despite the routine clinical use of bone cement based on PMMA as a fixing coating with antimicrobial activity for implants, it has several disadvantages and limitations. The main limit is the fact that this solution may only be applied to implants requiring bone cement fixation and this excludes, by definition, all cementless implants. Moreover, even in cemented prosthesis, several parts of the implants remain unprotected by the antibiotic-loaded cement mantle, as for example the polyethylene insert, the locking mechanisms and all the extra-medullary surfaces. A further limit consists of the limited number and concentration of antibiotic(s) that can be loaded to polymethylmethacrylate and the limited capability of bone cement to release the antibiotics. In particular, only antibiotics with sufficient thermal stability and water solubility can be used, at a concentration that should not exceed 0.5 to 2 g/40 g PMMA [34]. Research has been underway to develop methods to increase the antimicrobial activity of bone cement, for example, by adding silver-containing substances [35, 36].

GENTAMICIN PLLA COATING

A coating for tibial nails, composed of a poly-l-lactic acid (PLLA) matrix, loaded with gentamicin, was first introduced into clinical use in Europe approximately fifteen years ago. The coating provides 80% release of the antibiotic within the first 48 hours [37]. In the first published clinical report, Fuchs et al [38] observed no deep infections at six months' follow-up in 21 patients treated with a UTN PROtect Tibial Nail (DePuy Synthes, Bettlach, Switzerland) for closed or open tibial fractures, as well as for revisions. Metsemakers et al [39] reported a retrospective analysis, including nine patients with a Gustilo and Anderson grade II or grade III open tibial fracture, four infected nonunions, two acute tibial shaft fractures pretreated with external fixation, and one aseptic nonunion with a soft tissue defect. At 18 months' follow-up, no implant-associated deep infection was reported. Finally, in the most recent and largest study, data from four centres, analyzed the outcome of 99 patients with fresh open or closed tibial fractures or undergoing nonunion revision surgery [40]. At 18 months' follow-up, deep surgical site infection or osteomyelitis was noted in 4/55 patients (7.2%) after fresh fracture and in 2/26 patients (7.7%) after revision surgery. The heterogeneous material and the lack of a comparator makes the interpretation of these results particularly difficult.

Apart from the absence of comparative trials, a limit of this technology is the fact that it is only available for the tibia and for one specific nail design. Furthermore, screws and fixation holes are not protected by the coating, while gentamicin resistance, ranging from 2% to 50% in Europe [41], may reduce the efficacy of the coating in some cases.

THE DAC® HYDROGEL COATING

The "Defensive Antibacterial Coating" is the first antibacterial hydrogel coating specifically designed for orthopedic and trauma and maxilla-facial implants. Based on hyaluronic acid (HA), grafted to polylactic acid (PLA), it is applied at surgery directly on the implant or on the tissues to be protected from bacterial adhesion. Hyaluronic acid is a mucopolysaccharide, naturally occurring in all mammal organisms. Due to its high biocompatibility, and non-immunogenicity, HA is considered as an ideal biomaterial for medical and pharmaceutical use [42] and has several clinical applications in dermatology, aesthetic surgery, dentistry, urology, orthopedics and ophthalmology [43]. Local application of hyaluronic-based compounds has been demonstrated to be protective against various infectious agents, depending on HA concentration and molecular weight, while the ability of HA to reduce bacterial adhesion and biofilm formation has been recently reported [44]. High biocompatibility, safety profile and anti-adhesive properties make HA and its composites an attractive option to design a resorbable coating, aimed at reducing the impact of biofilm-related infections in various clinical settings.

In line with these premises and to design a sufficiently stable HA-based antibacterial coating for use in orthopedics, a combination of HA with polylactic acid was investigated [45]. In fact, PLA is a synthetic polyester, widely used for orthopedic implants [46]. The patented combination of the two biocompatible and biodegradable polymers did finally allow to obtain a chemical-physical stability of the coating that was considered optimal for implant protection, without any risk of side effects [47].

The sterile, bioabsorbable, implantable DAC® hydrogel is intended to be applied, at the time of surgery, as a protective barrier over the surface of an implantable device (e.g., orthopaedic prosthesis or fracture fixation devices), to prevent bacterial adhesion, colonization, and biofilm formation through physical means. The device may also be intra-operatively loaded with one or more antimicrobial agents to further enhance the killing of planktonic bacteria that may be eventually present.
The kit for orthopedics and trauma applications includes a prefilled syringe, containing the sterile DAC® powder, one complete set of sterile components (connector, backstop and spreader) and one empty graduated syringe (Fig. 2).

At variance with all other existing antibacterial coating technologies, the DAC® hydrogel has been designed to offer an "ALL IMPLANT(S)" coating ability and can be used to protect various surfaces, including titanium alloys, nickel-chrome, cobalt-chrome, stainless steel, hydroxyapatite, polyethylene or other polymeric biomaterials (Fig. 3).

The hydrogel is not designed and should not be mixed with bone cement or its components (polymethylmethacrylate, PMMA) until they have finished their exothermal reaction and have completely

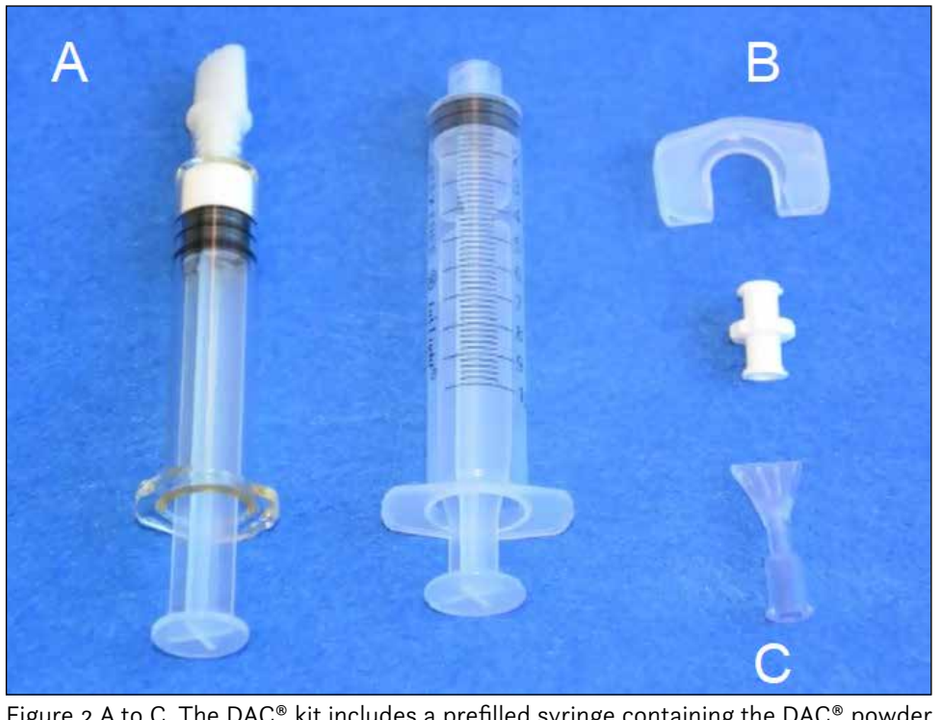

Figure 2 A to C. The DAC® kit includes a prefilled syringe containing the DAC® powder (A), a backstop and a connecting system for the hydrogel preparation (B) and a spreader to facilitate the hydrogel application on the implant surface (C), at the time of surgery.

hardened. The ability of DAC® hydrogel to completely cover even sand-blasted titanium surface and resist scraping has been confirmed by scanning electron microscopy (SEM) analysis [48]. Moreover, the DAC® coated implants can be press-fit inserted with the usual surgical technique. The resistance to scraping and de-clothing has been tested in the animal models and in human femurs, simulating a press-fit insertion of a cementless implant [49]. Both studies demonstrated the ability of the hydrogel coating to resist insertion, with approximately 60% to 80% of the hydrogel remaining adherent to all the implant surface, while the remainder being retrieved along the inner surface of the medullary canal.

In line with the concept of "ALL IMPLANT" coating, primary or revision cementless or hybrid joint prostheses and all internal osteosynthesis, including plates, screws and intramedullary nails, the surface in contact with the bone and all the modular parts, the polyethylene insert, the screws, sleeves, pegs, etc. and the respective locking mechanisms, should be protected with the hydrogel coating (Fig. 3).

Although the protection of the intra-medullary parts of an implant is pivotal, in order to prevent bacterial adhesion and proliferation at the implant-bone interface, defending the extra-medullary parts of the implant may be equally beneficial to reduce the chance of bacterial adherence and progressive colonization.

Furthermore, the antibiotic-loaded DAC® hydrogel coating can be successfully used in one-stage exchange procedure in peri-prosthetic infections [50]. However, in these cases, performing through debridement removing all infected and contaminated material remains paramount.
Preclinical studies have demonstrated the ability of the DAC® hydrogel to significantly reduce bacterial adhesion and biofilm formation of common bacterial pathogens, thus providing an effective protection of the implant [47, 48]. According to this finding, the antiadhesive hydrogel coating acts as a tool to reduce and delay bacterial adhesion and biofilm formation to a variable degree, depending on the local environment, the bacterial species and load. This activity of the coating may represent a key additional advantage to the host's cells to win the competition with the microorganisms that may eventually be present. Reducing the ability of bacteria to adhere to the implant will decrease

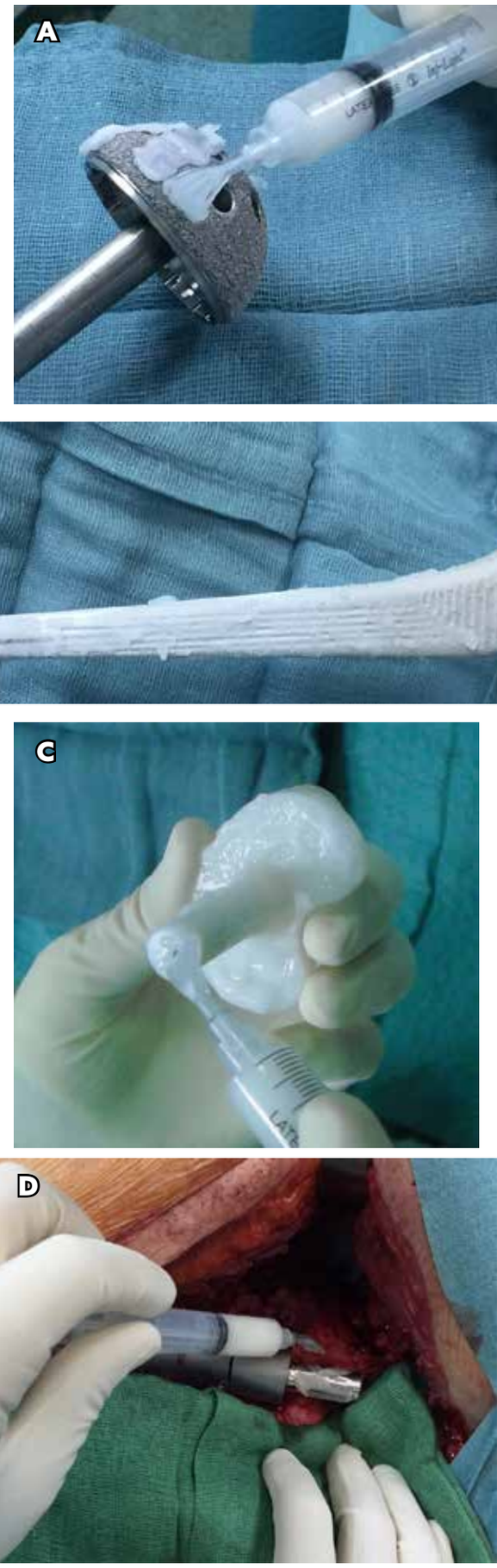

Figure 3 A to D. Examples of DAC® application on different implants: on a titanium acetabular cup (A), on a hydroxyapatite surface of a femoral stem implant (B), on a polyethylene insert of a revision knee prosthesis (C), and to the interlocking parts of a modular hip mega-implant (D).

the chance of bacterial colonization and infection, provided that the immune system and eventually the systemically administered antibiotic are able to kill the microorganisms in their planktonic state. Several studies have shown the effective antibiotic concentration in hydrogel ranges from 20 mg/mL to 50 mg/mL (2-5%), which is completely released within 72 hours of implantation [49]. (Table 4).

Moreover, microbiological analysis has demonstrated a synergistic antibacterial effect of the hydrogel-antibiotic combination, compared to either component alone [48. 49], while both preclinical [51, 52] and clinical studies do not report any adverse event or any detrimental effect on bone healing or implant osteointegration. In 842 patients, at an average follow-up of 21.4 months, the DAC® hydrogel coating has been shown to be associated with approximately 10 times reduction in post-surgical implant-related infections (Table 5).

CONCLUSIONS

Implant-related infections are projected to grow over the next decade. These are associated with increased rates of morbidity and mortality and have a significant social and economic impact on the society and health care systems. Despite the recognized need to curtail implant-related infection, only a few clinically applicable technologies are currently available in orthopaedics and trauma. Given the potential benefits that can be anticipated scientifically by a wider application of antibacterial implant coating technologies, with a well demonstrated positive cost-benefit ratio [58, 59], all effort should be made to increase the awareness of health care providers and implement the technology in health care systems to potentially mitigate the septic complication.

Furthermore, specific reimbursements for the currently available coatings should be introduced, with faster and more affordable regulatory pathways for the most promising technologies in the pipeline. At the same time, an efficient and independent post-marketing surveillance system need to be set at national or international level, to monitor the clinical results and promptly report on any possible side effect or long-term complication of such new technologies. ■

Antibiotic in powder form	Volume of sterile water for injection to be added	Volume of solution to be taken to reconstitute the DAC hydrogel
Vancomycin 500 mg	10 mL	5 mL
Vancomycin 1000 mg	20 mL	5 mL
Rifampicin 600 mg	15 mL	5 mL
Teicoplanin 200 mg	5 mL	5 mL
Teicoplanin 400 mg	10 mL	5 mL
Meropenem 500 mg	10 mL	5 mL
Meropenem 1000 mg	20 mL	5 mL
Cephazolin 1000 mg	20 mL	5 mL
Daptomycin 350 mg	10 mL	5 mL
Daptomycin 500 mg	10 mL	5 mL

Antibiotic in liquid form	Antibiotic vials	Volume of sterile water for injection to be added	Volume of solution to be taken to reconstitute the DAC hydrogel
Gentamicin 80mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 100mg / 2 mL	2 (= 4 mL)	1 mL	5 mL
Tobramicin 150mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Ciprofloxacin 200mg / 100 mL	1 (= 100 mL)	0 mL	5 mL
Ciprofloxacin 400mg / 100 mL	1 (= 200 mL)	0 mL	5 mL
Clindamicin 300mg / 2 mL	1 (= 2 mL)	3 mL	5 mL
Clindamicin 600mg / 4 mL	1 (= 2 mL)	1 mL	5 mL

Table 4. Charts showing the proportion of antibiotic and water for injection needed to intra-operatively reconstitute the DAC® hydrogel in order to load it with some antibiotics currently available in powder or liquid form.

	Average Follow-Up	CONTROLS		TREATED	
Author and date of publication	Months	Patients	Post-surgical infections	Patients	Post-surgical infections
Romanò et al. (2016) [53]	14.5	184	11	189	1
Malizos et al. (2017) [54]	18.1	127	6	126	0
Capuano et al. (2018) [50]	29.3	22	3	22	2
Zagra et al. (2019) [55]	30	27	4	27	0
De Meo et al. (2020) [56]	12	17	6	17	0
Zoccali et al. 2021) [57]	24	42	6	42	0
Total	21.4 ± 7.5	419	36 (8.6%)	423	3 (0.7%)

Table 5. Summary of data available from published comparative clinical studies, concerning DAC® hydrogel efficacy.

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THE USE OF STATIC SPACERS IN PERIPROSTHETIC KNEE INFECTIONS

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INTRODUCTION

The increasing number of total knee arthroplasty (TKA) being performed has led to a corresponding increase in the overall number of TKA infections. Periprosthetic knee infection is a severe and not infrequent complication, with an incidence ranging from 0.4 to 2.5% for primary TKA and 4 to 8% for revision surgery. The surgical treatment differs depending on the duration of the infection. The aim is to eradicate infection and maintain satisfactory knee function (range of motion, stability, no pain). For acute infection, prosthesis removal may not be necessary and a DAIR (Debridement, Antibiotics, Implant Retention) should be performed in association with exchange of the polyethylene insert.

For subacute or chronic infection, prosthetic replacement is necessary, and two methods of management can be discussed: single-stage or two-stage exchange arthroplasty [1, 2]. Single-stage exchange arthroplasty involves implant removal with debridement, followed by reimplantation of a new prosthesis during the same operation. Although single-stage exchange knee arthroplasty is possible in certain specific cases, prosthetic replacement in two stages is currently considered as standard treatment [3, 4, 5].

During two-stage exchange arthroplasty, the first stage is to remove all prosthetic material with thorough debridement of the periprosthetic tissues [6]. An antibiotic-impregnated cement spacer is positioned in place of the TKA implants. The optimal delay before the second surgery is still debated. The use of a cement spacer is practically systematic in the treatment of TKA infection using two-stage exchange. The spacer allows the preservation of sufficient joint space during the intermediate period without a prosthesis, which allows maintenance of the space for reimplantation of the new prosthesis during the second stage surgery. There are two types of spacers commonly used: static spacers or dynamic spacers. Both types of spacers have advantages and disadvantages. A good understanding of the spacer function and indications is critical for appropriate management of the two-stage exchange knee arthroplasty. Later, once the infection is controlled, prosthesis reimplantation is performed during the second stage.

In this review, we will discuss the characteristics of spacers, compare static vs mobile spacers, describe the indications and surgical technique using a static spacer followed by some case reports.

GENERAL SPACER PROPERTIES

A spacer is a temporary piece of organic cement [7, 8]. After removal of the infected implant and tissue, the principle is to create a cement-based replacement prosthesis, shaping them manually or using molds.

Mechanical properties

The role of the spacer is to stabilize the femoro-tibial joint during the intermediate time between surgical stages, to prevent knee dislocation and avoid pain. Adequate knee stability during this period protects the periarticular soft tissue, such as the extensor mechanism and avoids additional tissue injuries. It also limits arthrofibrosis filling the joint space and should prevent ligament and tendon retraction. Thus, using a spacer facilitates reimplantation surgery during the second stage [1, 9, 10]. Without the use of a spacer, soft tissues such as the ligaments shorten, possibly necessitating further bone resection, and leg shortening [1, 11, 12]. This will require creating space for reimplantation of a new prosthesis by performing extensive ligament release and implantation of a highly constrained or hinged prosthesis.

Anti-microbial properties

Whilst the patient is receiving appropriate systemic antibiotic therapy, spacers are also delivering high doses of antibiotics directly within the knee [8, 10, 13]. Systemic antibiotic therapy is active against the planktonic microorganisms but is not strong enough to eradicate the sessile forms protected by the biofilm [14]. The local diffusion of high doses of antibiotics contained within the spacer facilitates the eradication of the microbes in this biofilm and limits the development of secondary infection. The antibiotics present in cement are usually aminoglycosides such as gentamycin or tobramycin, or a glycopeptide such as vancomycin [8]. In our practice, we use high viscosity cement premixed with Gentamycin, and add Vancomycin. This combination has been shown to increase the release of both antibiotics locally [15-17]. The recommended dose is 1g of crystalline Vancomycin per 40 g cement package. The pharmacokinetic is well known [18]. The dose delivered locally is up to 700 times higher than when the dose is administered systemically [1, 19]. This level is significantly higher than the critical minimum inhibitory concentration (CMI) for antibiotic activity and avoids high systemic doses and associated complications.

The choice of antibiotics is important.

First, the antibiotic must be heat resistant, to be not destroyed during PMMA polymerization (up to 83°C for 13 min). The antibiotic must be water-soluble to be dispersed after implantation [2, 20, 21] and chemically stable when admixed with the cement. Vancomycin and Teicoplanin are both appropriate choices [10]. Powder form (crystalline) is preferred compared to the liquid formula, which risks decreasing the mechanical strength of the spacer by increasing porosity. Hsieh et al. [19] demonstrated that crystalline Vancomycin decreased mechanical resistance by 13% against 37% for liquid gentamycin. Even if the microorganism is identified, a combination of antibiotics is preferred to increase the target spectrum.

Two types of cement spacer

Antibiotic-impregnated cement spacers can be either static (non-articulating, block spacer) or dynamic [10]. Static spacers consist of a single block of cement inserted between the femur and the tibia (Case 1.B, 2.B, 3.B). It is non-articulating, fills the joint space and constitutes a temporary knee arthrodesis keeping the knee in full extension. This temporary immobilization leads amongst other things to joint stiffness and exposure difficulties at the time of reimplantation [9, 22, 23]. This increases the difficulty of prosthesis reimplantation and is associated with poorer clinical outcomes such as stiffness.

As a result, dynamic spacers have been developed with the aim of overcoming these problems. The dynamic spacer [24] consists of a femoral component articulated on a tibial baseplate. It is effectively a temporary prothesis made out of cement only or combination of metal, poly and cement. It features a smooth and congruent interface, the articulated spacers are designed to allow knee range of motion. Thus, it allows passive mobilization of the knee immediately following surgery. The dynamic spacer reduces the risk of muscular atrophy and retraction of the peripheral soft tissues and is associated with improved range of motion. In the absence of contraindications, the dynamic spacer should be preferred, because it improves the knee function, as well as postoperative mobility [22] and facilitates the exposure during the reimplantation but shows the same eradication rate compared to static spacers [22]).

COMPARISON STATIC VS DYNAMIC SPACERS

In the context of chronic TKA infections, several studies have compared infection management using articulated and static spacers. A meta-analysis published in 2017, including 10 studies, compared the effectiveness of static and dynamic spacers according to several criteria, specifically: rate of infection eradication, range of motion and functional scores, and soft tissue release during prosthetic reimplantation [26]. Since, few studies evaluated spacers outcomes [22, 27-29].

Rate of infection eradication

There is no significant difference between static and dynamic spacers [27, 29]. In a study of 81 static spacers and 34 dynamic spacers, Johnson et al. [30] found that the rate of infection eradication was 88% for the static spacer group and 82% for the dynamic spacer group. This rate was comparable in the two groups. Choi et al. [31] found lower, but comparable, infection eradication rates with 67% for the static spacer group and 71% for the dynamic spacer group. In a study by Brunnekreef et al. [32] 35 patients underwent two-stage revision surgery for chronic infection on TKA. The infection eradication rates were 100% for both the static and dynamic spacer groups. Thus, the rate of eradication of infection using a static spacer is between 67% [31] and 100% [30].

Range of motion

All studies tend towards better knee flexion after dynamic versus static spacers. Regarding range of motion, Park et al. [33] compared the clinical results of static and dynamic cement spacers for the treatment of infected TKA in 36 patients. They found a significant difference between groups: an average flexion at the last follow-up of 92° in the static spacer group versus 108° in the dynamic spacer group. In a study of 45 patients, Chiang et al. [34] reported similar results, with 85° of flexion in the static spacer group versus 113° in the dynamic spacer group. In the literature review by Hai Ding et al. [26], the average flexion at the last follow-up is between 74° and 98°. Flexion was significantly lower after static spacer use compared to dynamic spacer use [28].

Knee Society Score (KSS) and HSS Knee Score

All studies tend towards better functional outcomes after dynamic spacer compared to static spacer. Park et al. [33] and Freeman et al. [27] found an average KSS functional score of 50 and 45 points respectively in the static spacer group versus 76 and 70 points in the dynamic spacer group. Chiang et al. [34] and Park et al. [33] respectively found an average HSS score of 82 and 80 points for the static spacer group against 90 and 87 points for the dynamic spacer group. The functional scores at the last follow-up are comparable between different studies. These scores are significantly lower in the static spacer groups compared to the dynamic spacer groups. These findings were observed at 3.5years [22] and 5 years [28] follow-up.

Rate of surgical soft tissue release

Several authors have sought to assess the retraction of peripheral soft tissues during prosthetic reimplantation, and particularly the need to perform quadriceps tendon release or tibial tuberosity osteotomy (TTO). In a study of 28 patients, Hsu et al. [35] performed two rectus femoris snips and one Y-plasty of the quadriceps tendon during prosthetic reimplantation. They found that 29% of patients in the static group required a more extensive approach compared to only 5% of patients in the articulated group. Choi et al. [31] found that a more extensive approach was more frequently required in the static spacer group than in the dynamic spacer group (5 rectus femoris snips, 1 Y-plasty of the quadriceps tendon and 19 TTO in the static spacer group versus 3 rectus femoris snips and 1 TTO in the dynamic spacer group). Therefore, the use of articulated spacers facilitates the surgical exposure during the prosthetic reimplantation stage. The mobilization of the knee between the two surgeries avoids the retraction of the extensor mechanism and the articular capsule [36].

Complications

Johnson et al. [30] described complications requiring surgical revision due to dynamic spacers. Four of the 34 patients with dynamic spacers presented with mechanical failure and there were no failures of the 81 static spacers. Two patients with dynamic spacer failure that admitted to having resumed full weight

bearing presented with fractures of the femoral component. The other patients presented with a dislocation of the femoral component and a subluxation of the tibial component with skin breakdown who needed flap coverage. In a study by Streulens et al. [37], the dynamic spacer dislocated and caused significant knee subluxation in 7% of the patients. Only the posterior sagittal subluxation had an impact on KSS Function score. Subluxation do not decrease SF12 and WOMAC [38]. Wilson et al. [39] described a series of 3 complicated cases of anterior migration of the cement with partial or even total rupture of the patellar tendon following the implantation of dynamic spacers. In case of dynamic spacer risk could be reduced using postero-stabilized antibiotic cement with wire reinforced cam, which increased stability and decreased the risk of cam fracture [40]. Thus, static spacers have less risk of complications than dynamic spacers (Fig. 1).

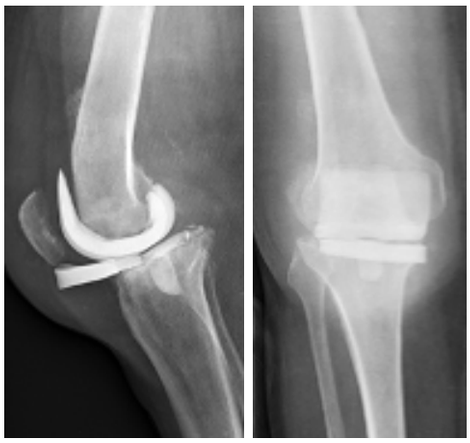


Figure 1: Radiographs of the knee of a 69-year-old man showing an anterior subluxation of the tibial mobile cement spacer.

INDICATIONS FOR A STATIC SPACER IN TKA INFECTIONS

The indications for a static spacer correspond to the contraindications of the dynamic spacer, specifically:

- Major bone loss, which is associated with a high risk of fracture, as well as a lack of fixation for a dynamic spacer (Cases 1-3).
- An incompetence of the collateral ligaments or the extensor mechanism, which can cause femoro-tibial dislocation with a dynamic spacer (Case 3).
- A skin condition at high risk of complications, needing a limitation of flexion or even immobilization of the knee to promote healing (Case 4).

Because of these exclusion criteria, the choice needs to be confirmed intra-operatively after an evaluation of soft-tissue and bone loss, to limit the risk of articular spacers for dislocation and extensor mechanism injuries [17].

SURGICAL TECHNIQUE STATIC SPACER

Step 1: Knee exposure

Exposure can be performed via a pre-existing scar or as per surgeon preference. After knee exposure, the level of the joint line is identified and measured relative to a drill hole which is made on the femur and the tibia at a safe distance from the joint level.

Step 2: Implants removal – Debridement

The prosthesis is carefully explanted, trying to save as much bone as possible. The bone loss should be described with the Anderson Orthopedic Research Institute (AORI) classification to prepare reimplantation.

Multiples tissues samples must be taken and sent for both microbiology and histopathological assessment. After sampling, the surrounding contaminated tissues are excised. The femoral and tibial intramedullary canals are reamed and cleaned. The reaming is important to clean the medullar canal but also to prepare the femoral and tibial shafts to receive the spacer. Then a thorough knee joint lavage (for example Pulsavac®) is performed using at least 9L of fluid.

Step 3: Making the static spacer

The firsts step is the fashioning of a rigid rod of cement reinforced by Kirschner wires to reduce the very high risk of spacer fracture. 3-4 wires of 2 mm diameter should be used and coated with high-viscosity antibiotic cement. When the mixture starts to solidify, it is molded manually by the surgeon (Fig.2). The length must be long enough to have at least 6 cm of rod in each femoral and tibial canal, plus the length of the joint space to bypass the joint and be stable and strong enough. Once set, this rod, marked at its center, is introduced back and forth into the femoral and tibial canals until the center mark is at the midpoint of the joint space (Fig.3). We usually use 1 cement package of 40 g for this rod.

Figure 2: Cement rod around 4 Kirschner wires

Figure 3: Introducing the cement rod into the femur, then the tibia, putting the mark at the center of the joint

	Date	Type of study	Number of dynamic / static spacer	Infection eradication	Range of motion	Mean KSS function score	Mean HSS score	Lengthening of the femoral quadriceps	TTO
Brunnekreef et al(4)	2013	Retrospective	9	100%	73.8°	-	-	-	55%
Chiang et al(6)	2011	Prospective	23/212	90%	85°	-	82	33%	-
Choi et al(2)	2012	Retrospective	14/33	67%	97°	-	-	18%	57%
Emerson et al(12)	2002	Retrospective	22/26	92%	93.7°	-	-	-	-
Fehring et al()	2000	Retrospective	30/25	88%	98°	-	83	8%	-
Freeman et al(7)	2007	Retrospective	48/28	89%	-	45	-	-	-
Hsu et al(8)	2006	Retrospective	21/7	85%	78°	57.8	-	28%	-
Johnson et al(3)	2012	Retrospective	34/81	82%	95°	-	-	-	-
Jämsen et al(13)	2006	Retrospective	24/10	75%	92°	53	-	-	-
Park et al(5)	2010	Retrospective	16/20	85%	92°	50	80	35%	4%

Table 1. Literature review of the use of dynamic and static spacers during two-stage prosthesis exchanges.

Next, the whole spacer is prepared using high-viscosity antibiotic cement. We use cement with Gentamycin and add crystalline Vancomycin, 1g per cement package. The Vancomycin should be added to the cement before being added to the liquid monomer [13]. If the Vancomycin is added later, the mixing is inconsistent due to poor dissolution and risks unequal diffusion into the soft tissues. We advise adding methylene blue to the preparation. We usually use 1 mL, added just at the start of mixing, to obtain a homogenous blue paste (Fig.4). The methylene blue is added to the cement to provide easy discrimination between native bone and cement and facilitate cement removal during the second stage of surgery [25].

Figure 4: Before and after mixing cement, antibiotics, and after adding methylene blue

The spacer should fill the joint space to maintain the native leg length. 2 minutes after the second cement mixture, the joint is opened with traction on the leg in extension to fill any bone defects and the joint space with cement. The size of the spacer should be appropriate but not too large to avoid excessive skin tension during wound closure. This second cementation stabilizes the construct and prevents spacer migration (Fig.5). The joint capsule, subcutaneous tissues, and the skin are closed in layers.

Step 4: Post-operative managment

Postoperatively, patients are kept in a brace in extension. Weight-bearing is not allowed.

During the second stage of surgery, the surgeon removes the cement by breaking the spacer and removing the rod spacer. It is easier to cut the wires and remove the rod in 2 parts. Another thorough debridement is performed and samples are taken before implantation of the new definitive prosthesis.

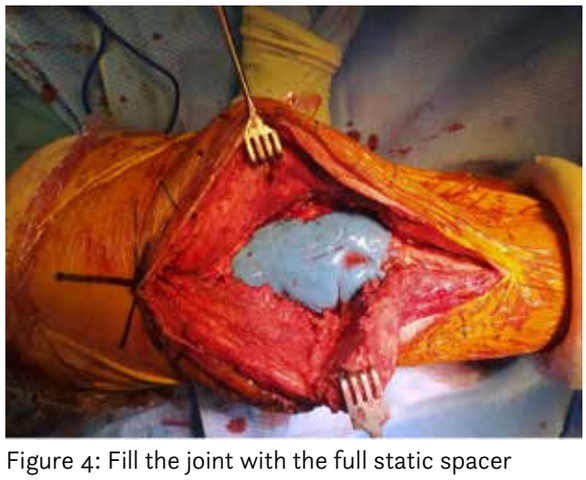
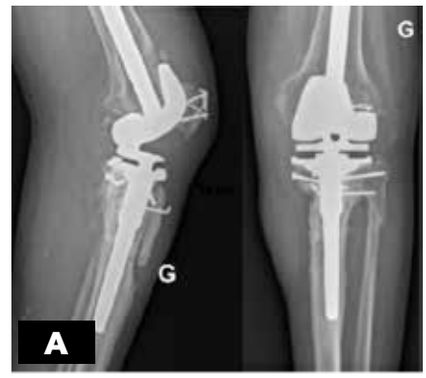


Figure 4: Fill the joint with the full static spacer

CASE REPORTS

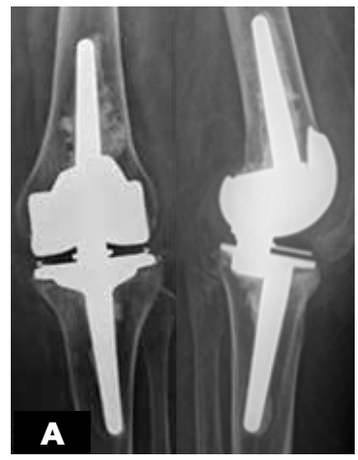
Case 1

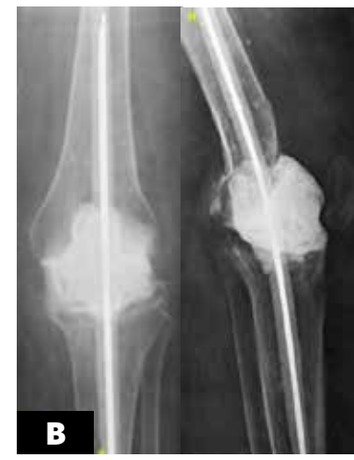
A 36-year-old man had septic loosening of his revision TKA, major bone loss mainly on the tibia and chronic rupture of the partial extensor mechanism allograft.
Bone loss and failed extensor mechanism allograft lead to static spacer.
A. Radiograph before revision showing loosening.
B. Radiograph after insertion of the static spacer.
C. Radiograph after reimplantation of a hinge knee prosthesis with extensor mechanism reconstruction including proximal tibia allograft.

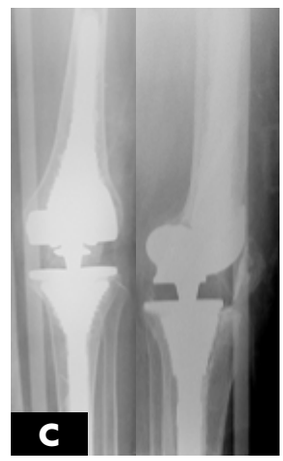


Case 2

A 57-year-old man had septic loosening of his revision TKA and chronic rupture of the quadriceps tendon. After removal of the TKA, there was major femoral and tibial bone loss.
Bone loss and deficient extensor mechanism lead to static spacer.
A. Radiograph before revision showing loosening.
B. Radiograph after insertion of the static spacer.
C. Radiograph after reimplantation of a hinge knee prosthesis, associated with reconstruction of extensor mechanism using the Hanssen mesh technique.

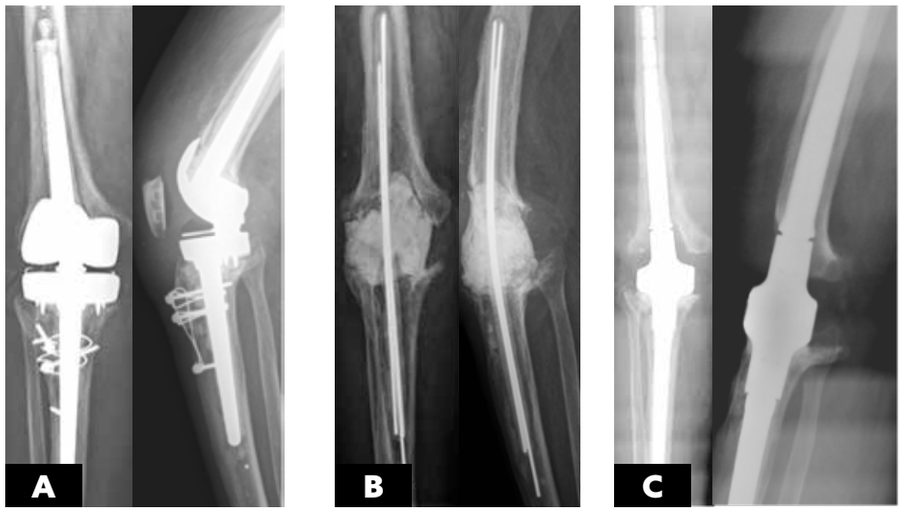






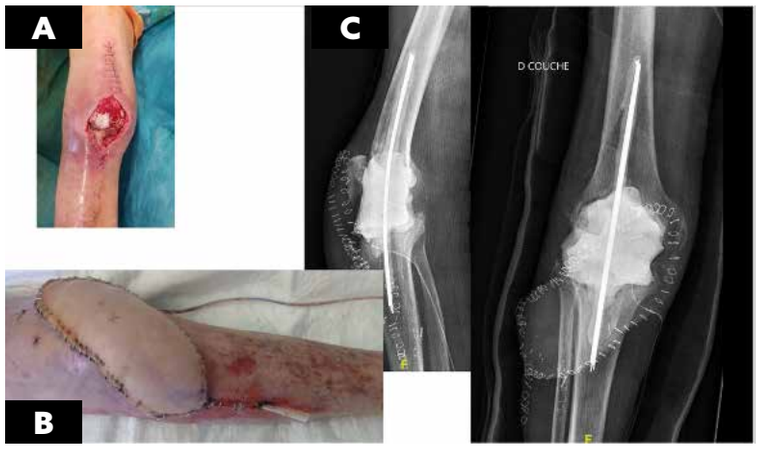
Case 3

A 69-year-old man had chronic sepsis of his revision TKA and rupture of the allograft extensor mechanism. Bone loss and deficient extensor mechanism allograft lead to static spacer.
A. Radiograph before revision.
B. Radiograph after insertion of the static spacer with reinforcement Kirschner wires.
C. Radiograph after reimplantation of an arthrodesis prosthesis at the second stage revision.



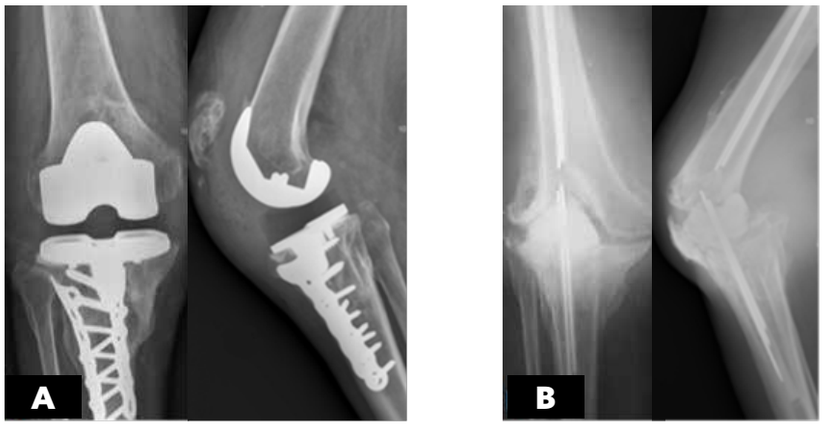
Case 4

The hazardous skin evolution leads to a static spacer to allow good healing of the free flap.
A. Picture of the skin loss after debridement.
B. Picture of the skin cover, using free flap.
C. Radiograph after insertion of the static spacer, used to protect the flap.



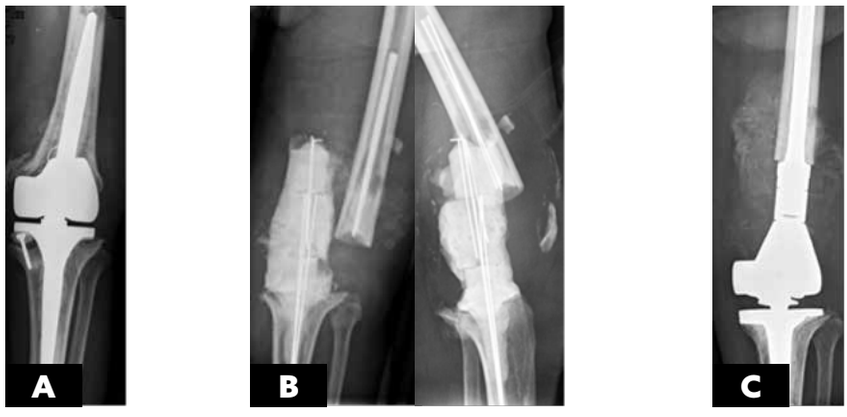
Case 5

A 69-year-old man had chronic sepsis of his TKA with chronic rupture of the patellar tendon
A. Radiograph before revision.
B. Radiograph after the first stage revision showing a broken static cement spacer.



Case 6

A 75-year-old man had chronic sepsis of his TKA with major femoral bone loss.
A. Radiograph before revision.
B. Radiograph showing a broken massive static cement spacer.
C. Radiograph after reimplantation of rotating hinge distal femoral replacement prosthesis during the second stage revision.



CONCLUSION

Two-stage prosthetic replacement, with the use of a cement spacer during the intermediate phase, is currently considered as the gold standard treatment for chronic prosthetic knee infections. During prosthetic reimplantation, static spacers are associated with retraction of peripheral soft tissue and greater difficulty in surgical exposure. This difficulty in exposure is related to the immobilization of the knee during the intermediate phase and may require an important soft tissue release. The use of a static spacer impacts the functional knee results of patients.

Articulated spacers allow limited knee mobilization between the two surgical stages and can facilitate the ease of prosthesis reimplantation during the second stage. However, the dynamic spacers are associated with a greater number of complications compared with static spacers, particularly in cases of improper use.

When contra-indications for a dynamic spacer are present (major bone loss, knee instability with collateral ligament or extensor mechanism incompetence and precarious skin condition) a static cement spacer is preferred. In order to minimize the risk of complications of spacers during the intermediate phase, the surgical technique and the indications of each type of spacer must be well known and understood. ■

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JOINT ARTHROPLASTY IN SEQUELAE OF SEPTIC ARTHRITIS OF THE HIP: A THERAPEUTIC GUIDELINE TO SINGLE OR TWO STAGE PROCEDURES

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INTRODUCTION

Acute septic hip arthritis can nowadays be treated initially with arthroscopy or open debridement, followed by appropriate antibiotic therapy, but success or failure at preserving the joint are closely related to time elapsed since initiation of symptoms, with a cut-off at about 1 to 2 weeks (1). In cases where the symptomatic period is prolonged and radiologic evidence of articular destruction is present, more radical surgery is needed. Articular resection is needed to eradicate infection, but it is associated with postoperative morbidities like leg length discrepancy, use of walking aids and use of pain medication. Historically, deep prosthetic infection was treated with resection arthroplasty (Girdlestone procedure), but the appearance of antibiotic loaded cement spacers allowed for better joint function with increased local antibiotic concentration. Better soft tissue tension permits full weight bearing and will facilitate the subsequent revision and articular reconstruction. (4,5,6)

The most feared complication in hip arthroplasty after septic arthritis (active or quiescent) is recurrence of infection. A two-stage protocol, using a spacer and replacing it with a definitive prosthesis in a second stage once the infectious process is resolved, is considered the accepted treatment for acute septic arthritis of the hip. However, treatment in one stage is accepted for quiescent septic arthritis, taking as parameters of absence of infection the following conditions: clinical status, normalization of laboratory values (ESR and CRP) and time elapsed between the resolution of the infection and the moment of joint replacement. In these cases, the microorganism responsible for the primary infection has no relevance, as long as the times of treatment and quiescence have been respected as described by Kim et al (7)

The purpose of this paper is to establish, , a therapeutic guideline for septic arthritis on native hips, proposing treatment in two stages for acute septic arthritis and in one stage for quiescent cases. The guideline is based on our experience with cases treated at our institution during the last 25 years.

PATIENTS & METHODS

We conducted an observational, descriptive, retrospective study, analysing all patients with primary total hip replacement between June 1997 and June 2016, selecting those that had a diagnosis of septic arthritis prior to surgery and divided them into two groups.

Group 1: acute septic arthritis
defined as patients with a clinical presentation of severe spontaneous pain that increases with joint motion, load intolerance, fever, erysipelatous inflammation, swelling, altered laboratory parameters (leukocyte count, ESR and CRP), radiological evidence of usually rapid joint line narrowing and later bone destruction (Figure 1), MRI changes and finally, a positive culture in joint aspiration

Group 2: quiescent septic arthritis
definition of quiescent septic arthritis is reserved for patients with a history of acute septic arthritis, who have completed antibiotic treatment, have normal laboratory values and absence of clinical signs that suggest ongoing infection. These patients present clinical and/or radiological signs of articular damage (Figure 2) that require joint replacement.

We excluded patients with a follow-up of less than one year and those who had a previous internal fixation or prosthesis in the affected joint or adjoining to it. For this reason, infected acetabular and/or femoral osteosynthesis, a not unusual finding, were not included. In the period 1997-2016, 6263 primary hips were operated. The population studied includes 20 patients with 22 hips (2 bilateral) with a diagnosis of septic arthritis of native hip, either acute or quiescent, treated with total hip arthroplasty

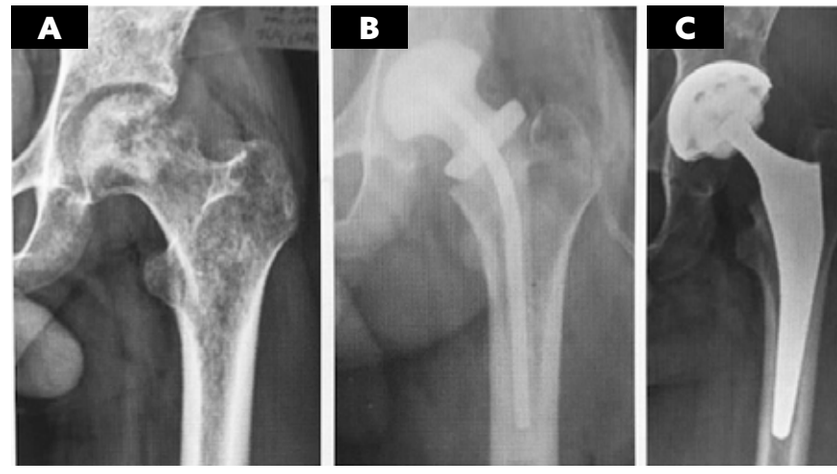

Figure 1: A. Acute septic hip arthritis of 6 weeks duration, with regional osteopenia, joint narrowing and lytic changes in the femoral head. B. First stage. Antibiotic loaded Cement spacer. C. At three months, final implant

and with a follow up greater than one year. Data included pre- and post-operative Harris Hip Score, previous treatments, and microbiological data when available (Tables 1 and 2).

Patients in group 1 with evolving septic arthritis (9 hips in 8 patients) had hip joint aspiration to identify the causative microorganism. Subsequently, they were treated in two stages. The initial surgical procedure was carried out through an anterolateral approach with extensive synovectomy, resection of the femoral head and acetabular reaming for removal of remaining articular cartilage. Three to six samples for culture and antibiogram were obtained. A hand made (3 hips) or preformed (6 hips) antibiotic (ATB) loaded spacer was placed, generally with Gentamicin and, in case of adding cement, this was mixed with Vancomycin (1 to 3 grams). Patients continued with intravenous antibiotic treatment and then orally for a minimum of 6 weeks, as established by the Infectology Dept. The second stage took place once the laboratory values (ESR and CRP) yielded normal twice, without ATB treatment, with an interval of two weeks between them. Once remission of infection was ascertained, final reimplantation was performed. The type of prosthesis to be used (uncemented, hybrid or cemented) was selected according to age, functional demand, and bone quality. Systemic AB were used for 24 hours only and in cases of hybrid or cemented implants, ATB added to cement was used as infection prophylaxis (no more than 1 g per dose of cement), but not as a treatment for the infection since the infection was considered resolved before performing the joint replacement procedure. (Figure 1 A to C).

Group 2 includes patients with a history of previous septic hip arthritis and considered in remission of infection (13 hips in 12 patients). These patients were free of infection for at least two years since the end of treatment, had normal laboratory values and favourable clinical outcome. In them, one stage arthroplasty was performed, using the usual antibiotic prophylaxis scheme as for primary hips (1/2 gr IV cefazolin at anaesthetic induction and during the first 24 hours after surgery). All femoral heads were sent to culture. No previous joint aspiration was performed since, as described by Bauer et al (3), it serves no purpose in detecting eventual persistent infections of low virulence in quiescent septic arthritis, which explains the high number of false negatives reported by the authors (Figure 2 A and B). In our protocol, we do not consider the use of postoperative antibiotic schemes different from the primary hip protocol.

Patient	Gender	DOB	Germ	Spacer	Weeks of AB	Arthroplasty
FJ	M	7/31/39	S. pneumoniae	08/16/11	9	6/12/11
SG	F	11/22/41	S. pneumoniae	08/05/15	8	15/10/15
CM	F	1/1/75	Bacteroides sp.	03/31/15	12	7/7/15
PC	M	4/1/76	MSSA	02/17/16	8	23/5/16
GM	M	5/10/94	MSSA	08/06/15	11	11/12/15
GM	M	5/10/94	MSSA	08/06/15	11	11/12/15
CA	M	1/11/57	MSSA	06/14/16	6	15/9/16
DM	F	5/12/48	S. pneumoniae	03/11/15	8	4/6/15
GB	F	6/24/89	MRSA	11/10/18	10	22/2/19

Table 1: Group 1 (acute septic arthritis)

Patient	Gender	DOB	Age of Infection	Quiescent years	Arthroplasty date
LA	M	4/2/44	15	38	29/7/97
SA	F	12/12/55	40	5	18/9/01
SM	M	12/3/47	12	46	1/6/05
PS	M	25/10/59	11	37	18/3/08
FP	M	5/10/76	13	19	17/02/2009
PC	F	20/7/29	48	33	9/8/10
DE	F	4/12/96	Neonatal	16	26/6/13
DE	F	4/12/96	Neonatal	16	26/6/13
CF	M	27/11/79	8	27	15/5/15
PS	F	2/4/74	10	30	6/10/14
SE	F	11/1/84	Neonatal	31	26/7/16
GV	M	9/11/69	45	3	6/12/17
CP	F	22/7/65	8	45	20/5/18

Table 2: Group 2 (quiescent septic arthritis)

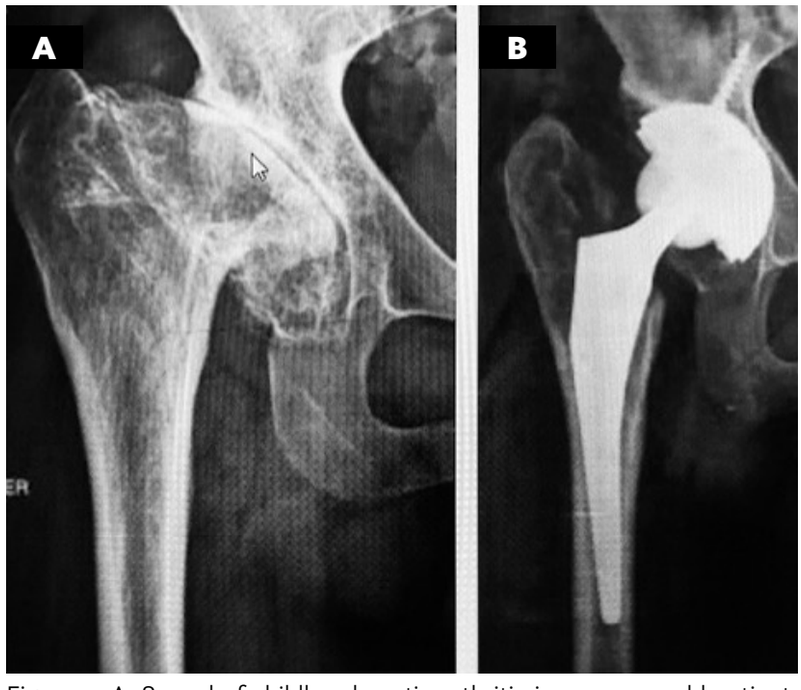

Figure 2: A. Sequel of childhood septic arthritis in a 37-year-old patient. (Quiescent). B. One stage treatment with uncemented arthroplasty.

In acute septic arthritis, a successful treatment is defined as eradication of infection after the spacer has been implanted with normalization of ESR and CRP, and, in quiescent septic arthritis, the nonrecurrence of infection after the definitive implant. The pre- and post-operative functional results were analysed with the Harris Hip Score.
Statistical analysis: quantitative variables were described by means and standard deviation, and categorical variables by percentage. The differences in the quantitative variables between the test groups were compared with the differences between proportions with the x^2 test. Statistically significant differences are probabilities less than 0.05. Statistical analysis was performed with STATA version 13.0 software.

RESULTS

Group 1 (acute septic arthritis) included 9 hips in 8 patients (one bilateral), four women and four men with an average age of 49.25 (21 to 74) years at the time of diagnosis, and an average follow-up of 4.25 (1 to 12) years. Isolated germs included Staphylococcus aureus in five cases (1 resistant to methicillin), Streptococcus pneumoniae in three, and Bacteroides spp in one. All patients underwent specific antibiotic treatment from six to 12 weeks (avg 9 weeks) between the placement of the spacer and the final prosthetic replacement (Table 1). Before Reimplantation antibiotic treatment was discontinued for 30 days. Remission of the infection was verified by a satisfactory clinical outcome with normal values for ESR and CRP.
In all cases the infection could be eradicated and the clinical results were satisfactory in all cases, with a notable gain in function and absence of pain, improving from an average HHS of 22 points before the initial surgery, to an average HHS of 93 at 6 months after reimplantation. This result showed to be statistically significant in favour of group 1 (p 0.001). No postoperative complications or exacerbation of the infectious process were observed until the present date.
Group 2 (quiescent septic arthritis) included 13 hips of 12 patients (one bilateral), seven women and five men, with an average age of 49.2 (16 to 81) years at the time of surgery. Time elapsed between infection and prosthetic replacement varied between five and 46 (average 18.8) years. Femoral heads sent to culture were in all cases negative. Functional results from the Harris Hip Score in this group improved from an average initial value of 37 points, to an average end of 88 points (Table 2). Some patients remained with certain limitations in their range of motion, as a consequence of stiffness after so many years of evolution that generated soft tissue retraction. However, they all evolved with a significant functional improvement of the joint. The postoperative follow-up of the patients of both groups was not different from the usual one for all patients with total primary arthroplasty in our centre. Postoperative controls were carried out at the third and eighth week, and then at 6 and 12 months and annually from there on. No follow up nor postoperative laboratory studies were ordered by the infectology department because these were considered patients with infectious disease resolution, and all had infectious discharge prior to joint replacement.

DISCUSSION

Primary septic arthritis of the hip in adults is a rare but potentially devastating condition (2). When undertaking this study, it became clear the need for and importance of differentiating and defining acute and quiescent septic arthritis, thus treating them as different entities with their diverse preoperative evaluation, treatment, and follow-up.
In acute septic arthritis, symptomatology is that of an active infection and treatment goes in that direction. For quiescent arthritis, treatment is that of the sequel of a joint infection with its destruction. The high cure rate allowed by antibiotic cement spacers and their greater efficacy has been demonstrated for years as compared to that of previous procedures such as antibiotic cement beads. Spacers preserve joint function and facilitate revision for the treatment of prosthetic infection, but a protocolized treatment that differentiates acute septic arthritis from quiescent septic arthritis in native hips has not been described previously.
Whatever the bacteria involved (pyogenic or mycobacteria), the role of arthroplasty in these pathologies remains clear. The risk of complications, and especially of failure due to persistence of infection in acute septic arthritis or due to exacerbation in quiescent ones is difficult to determine (8) despite not having, in our results, patients with postoperative infection or recurrence.
Referring specifically to acute septic arthritis, Jupiter et al. suggest that arthroplasty can be performed in one time, either for acute or quiescent septic arthritis, obtaining results comparable to those obtained in a two-stage treatment (9). Anagnostakos et al. describe a high rate (87%) of control of acute septic arthritis with two-stage treatment, but also highlight the high mortality rate between the first and second stage (8.8%) (2). Bauer et al.(3) resolved 85% of cases by a two-stage protocol for acute septic arthritis of 13 joints, taking into account that these authors evaluated hips and knees equally.
Our choice of a two-stage treatment for acute septic arthritis was to perform initial infection control by treating the condition with thorough joint debridement and an antibiotic loaded cement spacer. Previous joint aspiration in these cases is mandatory to identify the microorganism. In these cases, we consider that the treatment of choice is surgical debridement with removal of the femoral head, antibiotic treatment local with the spacer and systemically until normalization of laboratory values, then proceeding to the final implant. This allows greater predictability in the results and practically ensures the placement of a prosthesis in an infection free joint.
In relation to hips with history of infection that we call quiescent, treatment consists in solving the sequelae of a joint that is usually severely damaged. There are some guidelines that must be taken into account. First to have a normal laboratory with regard to infection (normal ESR and CRP) and second minimum two years that the infection has been in remission (10,11).
According to Kim et al. (7), the longer the symptom-free interval between the initial infection and the arthroplasty, the higher the success rate and the lower the risk of reinfection. Another point to highlight is the preoperative biopsy that, in the case of active infection in acute septic arthritis, is mandatory to diagnose and identify the pathogen involved. However, as described by Bauer et al., where they obtained seven false negatives in 23 patients, it does not apply to detect theoretical persistent infections of low virulence in quiescent septic arthritis (3). In our series, prior joint aspiration does not seem to be strictly necessary. In the group of patients with sequelae of septic arthritis, aspiration was not performed routinely, and the small usefulness of this procedure was reflected in the fact that femoral head cultures were all negative.
Similarly, functional recovery of patients with acute septic arthritis was different compared to quiescent. Patients with the acute condition presented a better functional recovery and this is mainly because patients with septic arthritis sequelae have

an interval of years between the treated infection and the prosthetic implant and may even have previous surgeries (12) with soft tissue retraction, anatomical alterations of the joint and muscle atrophy. We believe that one stage joint replacement in quiescent arthritis is the method of choice. Bauer et al. obtained a 100% success rate through one stage arthroplasty for nine quiescent hips (3).

In our series, the result was highly satisfactory with this procedure, also obtaining 100% good results. The same authors propose, in quiescent septic arthritis, to associate postoperative antibiotic therapy until the results of the cultures are obtained (3). In our protocol, we do not include any antibiotic scheme beyond that used for the prophylaxis of infection that is carried out for primary arthritic hips. All femoral heads were sent to culture, and all yielded negative results. However, the use of such femoral heads as a source of bone graft is not recommended.

The main weakness of our series is that it is retrospective and has a limited number of patients, which nonetheless coincides with numbers published in other papers. Despite this, we believe it presents considerable strengths: in all cases, the same protocol was applied; the cases are consecutive, all corresponding to the same joint, not comparing hips and knees; and it is original considering it as a national publication. This work may be considered as an important starting point in the study of two pathologies that, even though they can be mistakenly interpreted as one, must be considered, evaluated, and treated differently.

CONCLUSIONS

In our experience of the last 20 years, we have obtained satisfactory results, that is why we believe it is possible to establish a therapeutic protocol for primary septic hip arthritis, in two stages for active infections, with the placement of an antibiotic loaded spacer in a first stage, followed by a period of not less than six weeks of antibiotic treatment, and, once the values of ESR and CRP have been normalized, the placement of the definitive hip prosthesis.

The treatment in one stage for quiescent infections with at least two years between the remission of the infection and the placement of the implant, is the one of choice, verified by already negative values of ESR and CRP, with the placement of the definitive hip prosthesis.

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ISSN : 2658-9877

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SEPTIC ARTHRITIS OF THE KNEE JOINT IN AZERBAIJAN: A 5-YEAR RETROSPECTIVE MICROBIOLOGICAL INVESTIGATION

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INTRODUCTION

Musculoskeletal infection remains a major issue in orthopedics, posing complex diagnostic and therapeutical dilemmas and being associated with high economical and social costs [1-3]. In fact, musculoskeletal infection remains a major problem not only for traumatologist-orthopedists, but also for microbiologists [7-9], with a lack of universally accepted therapeutical approach, due to the relative scarcity of scientific evidence [3]. Among the many challenges of bone and joint infections, the relative frequency of antibiotic-resistant strains in different clinical conditions and in the various geographical areas remains largely unknown [1,4-6].

To fill the gap, in 2017 the World Association against Infection in Orthopedics and Trauma (WAIOT) was established in Vienna, with the mission to increase and disseminate the scientific knowledge on bone and joint infections worldwide. Among the various targets, a WAIOT task force decided to start investigations on the microbiology of large joints infections in some underreported geographical areas. In fact, septic arthrtitis of large joints is a serious condition, that, if not appropriately treated in a timely manner, may lead to severe and permanent joint damage, with loss of function and the need for complex joint reconstruction surgeries [10].

The knowledge of the most frequent pathogens causing joint infections in a given geographical region may then play a strategic role to choose the most appropriate empiric antibiotic treatment, while waiting for cultural examination results [11-15]. Given the scarce reports about the microbiology of native knee joint infections in Azerbaijan and surrounding countries [16], as a part of the larger investigation, we here report the data of a cohort of patients, affected by knee septic arthritis, admitted to a one orthopedic referral center in Baku, Azerbaijan over the last 5 years.

MATERIALS AND METHODS

This study was designed as a retrospective analysis of 54 patients (39 males, 15 females), affected by septic arthritis (SA) of the knee and treated at a one orthopaedic center in Baku, Azerbaijan, from 2014 to 2019. Thirthy-nine patients (72.2%) were male and 15 (27.8%) female. Mean age was 43.8±4.9 years (min. 5, max. 77). Seven patients (13%) were treated conservatively and 47 (87%) underwent surgical treatment. Etiology of septic arthritis are showed in Tab.1.

The high value of steroid septic arthritis associated with intra-articular injection of the steroid drugs - (25.9%) is noteworthy. Patients were classified according to the criteria described by J.H. Newman (1976) [17] (Tab.2) with some modifications, as follows:
s
1. Septic arthritis and steroid septic arthritis (SSA) without involvement in bone tissue:

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

Etiology of septic knee arthritis	All septic arthritis %
After injury	19 (35.2)
Hematogenous	7 (12.9)
After intraarticular steroid injection	14 (5.9)
Postoperative	5 (9.3)
Other or unknown etiology	9 (16.7)

Table 1. Etiology of septic knee arthritis of the patients included in this series.

Arthritis	All arthritis	All osteoarthritis	SSA	SSOA	SA	SOA
n=54	n=40	n=14	n=9	n=5	n=31	n=9
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%)		-
Total 54	40 (74%)	14 (26%)	9 (16,7%)	5 (9.2%)	31 (57.4%)	9 (16.7%),

Table 2. Classification of arthritis: Patients were sub grouped into four categories: steroid septic arthritis (SSA), steroid septic osteoarthritis (SSOA) (infection following steroid injection into joint, with cartilage and/or bone damage caused by the infection), septic arthritis (SA) and septic osteoarthritis (SOA)

2. Septic osteoarthritis and steroid septic OA (SSOA) with involvement of bone tissue according to radiological methods of examination:
Group D: positive synovial fluid cultures or from material taken during surgery
Group E: negative cultures, but pronounced clinical signs of local inflammatory process, correlating with laboratory data

Microbiological samples were obtained by joint aspiration and swabbing of wounds during surgery. The biological samples taken from patients were cultured in proper agar plates and broth media. In particular, the purulent samples collected by swabs and the aspirated synovial fluids were seeded in differential-selective medium, as blood agar plate, mannitol sal agar (MSA for diagnosis of staphylococcus), eosin methylene blue (EMB for diagnosis of enterobacteria), Saburoud agar for diagnosis of candida and ifomycetes. Mono and polymicrobial cultures were analyzed and compared with clinical symptoms and other biochemical tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Each microorganism was isolated and identified. Microbial characterization was conducted by biochemical and phenotypical microbiological methods to determine the species and gender of gram-negative and gram-positive isolates. Susceptibility of isolates to different antibiotics were tested following Kirby Bauer disc diffusion method [18] using Muller Hinton Agar against selected antibiotics. Most antibiograms included MICs to determine the most effective antibiotic that will result in effective treatment. After 16 to 18 hours of incubation, each plate was examined, the diameters of the zones of inhibition (as judged by the unaided eye) are measured, including the diameter of the disc. Zones are measured to the nearest whole millimeter, using sliding calipers or a ruler, which is held on the back of the inverted Petri plate. Inhibition zone size was interpreted using standard recommendation of Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement (January 2007, M100-S17 Vol. 27 No. 1 Replaces M100-S16 Vol. 26 No. 3)

Statistical data processing was performed using the computer program Statistica 12.5. The results are presented in the form M±SD , where M - is the arithmetic mean, SD - is the standard deviation and are calculated on an online calculator. All subjects gave their informed consent for inclusion before they participated in the study. The study was approved by the Azerbaijan Research Institute of Traumatology and Orthopedics Ethical Committee.

RESULTS

The etiologies of septic arthritis are shown in Tab. 1. Of note, 25.9% of the infections were subsequent to an intra-articular steroid injection and 9.3% were post-surgical. Thus, in 35.2% of patients, septic arthritis arose because of medical manipulations. According to the Newman criteria, 40 (74%) patients did not show radiographic signs of bone involvement; in particular, 31 (57.4%) were classified as Group A infections, 4 (7.4%) as Group B and 5 (9.2%) as Group C. Of the remaining patients, 12 (22.2%) were identified as Group D and 2 (3.7%) as Group E.

A positive culture was found in 43 cases (79.6%) and negative in 11 (20.4%) cases. Among positives cases, a single pathogen was detected in 12 (27.9%) patients, 2 pathogens were isolated in 17 patients (39.5%), and 3 pathogens were isolated in 14 patients (32.6%). Overall, 86 strains were isolated in 43 patients. The most common single isolated pathogen was Staphylococcus aureus, while the less often retrieved was Streptococcus pyogenes. If we take all cases of mixed microflora as 100% then mixed florae consisted of two microorganisms was found in 17 (54.8%) of patients, while infections with three microorganisms was found in 14 cases (45.2%). Most common associated microorganisms in two and three polymcrobial isolates were *Staphylococcus aureus, Candida albicans and Staphylococcus epidermidis, Candida albicans, Escherichia coli* respectively (Tab 3).

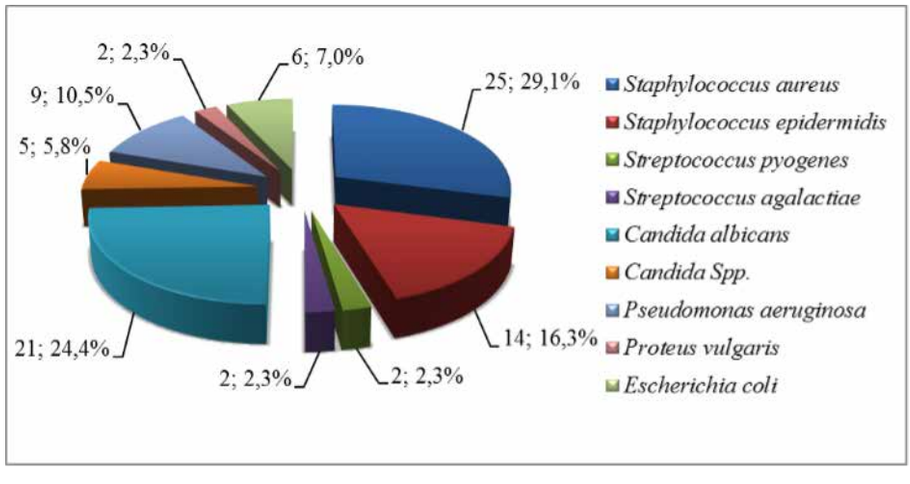
Considering the overall relative frequency of the isolated microorganisms, facultative anaerobe Gram-positive cocci were: *Staphylococcus aureus* (29.1%), *Staphylococcus epidermidis* (16.3%), *Streptococcus pyogenes* (2.3%), *Streptococcus agalactiae* (2.3%); facultative anaerobe Gram-negative bacilli were: *Escherichia coli* (7%), *Proteus vulgaris* (2.3%); anaerobe non-fermentive Gram-negative bacillus as *Pseudomonas aeruginosa* (10.5%); endosymbiotic fungi as *Candida spp.* (5.8%), *Candida albicans* (24.4%) (Diag. 1).

The overall incidence of mixed florae was 72.1% interestingly, the incidence of patients affected by the infection due to a mixed flora was 16.3% (7/43) in patients treated conservatively and 83.7% in those treated surgically.

In reviewing the results for each group, it is clear that in patients with SOA, the results were 100% positive and found only in mixed florae form. In patients with SA (n = 31), treated conservatively (7/31) negative microflora was not obtained. In patients treated operatively (24/31), neg-

Microbial results (n=43 patients)	Number (%)
Mixed-culture (2 microrganisms)	
Staphylococcus aureus, Candida albicans	6 (19.3)
Staphylococcus aureus, Pseudomonas aeruginosa	3 (9.7)
Staphylococcus epidermidis, Candida albicans	3 (9.7)
Staphylococcus epidermidis, Candida spp.	2 (6.5)
Staphylococcus aureus, Streptococcus pyogenes	1 (3.2)
Staphylococcus aureus, Candida spp.	1 (3.2)
Staphylococcus epidermidis, Pseudomonas aeruginosa	1 (3.2)
Representativeness error (M±SD)	2.4±1.8
Mixed-culture (3 microorganisms)	
Staphylococcus epidermidis, Candida albicans, Escherichia coli	5 (16.1)
Staphylococcus aureus, Staphylococcus epidermidis, Candida albicans	2 (6.5)
Staphylococcus aureus, Streptococcus agalactiae, Candida spp.	2 (6.5)
Staphylococcus aureus, Candida albicans, Proteus vulgaris	2 (6.5)
Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans	1 (3.2)
Staphylococcus aureus, Candida albicans, Escherichia coli	1 (3.2)
Staphylococcus epidermidis, Pseudomonas aeruginosa, Candida albicans	1 (3.2)
Representativeness error (M±SD)	2.0±1.4
Representativeness error (M±SD) (all mix-culture)	2.2±1.6

Table 3



Diag. 1: Relative frequency of isolated microorganisms (n=86).

ative culture responses were found in 3 (12.5%) cases. (Tab. 4).

Patients treated conservatively showed most often a single pathogen (5/7; 71.4%), compared to those treated surgically, in which a single microorganism was found in only 5/47 cases (10.7%), while the remaining showed a mixed flora (29/47; 61.7%) or a negative culture (11/47; 23.4%). The frequency of incidence of microorganisms is related to the duration and phase of the disease. (Tab. 5).

In patients with SSA in the acute phase (up to 2 weeks from the moment of injection), the number of isolated strains of microorganisms was significantly less than in patients in the acute phase of normal SA. In patients with the chronic phase of SSA, 5 strains of microorganisms were isolated, which is significantly less than in patients with SA - 8 strains.

Interesting data were obtained by correlating the data of positive microbiological tests depending on the type of pathology and etiology of the knee arthritis. In 40% of the patients with SSOA and in 66.7% of the patients with SSA the cultures were negative. Is it possible to interpret the inflammatory process as aseptic in this group of patients? We cannot answer this question yet (Diag.2).

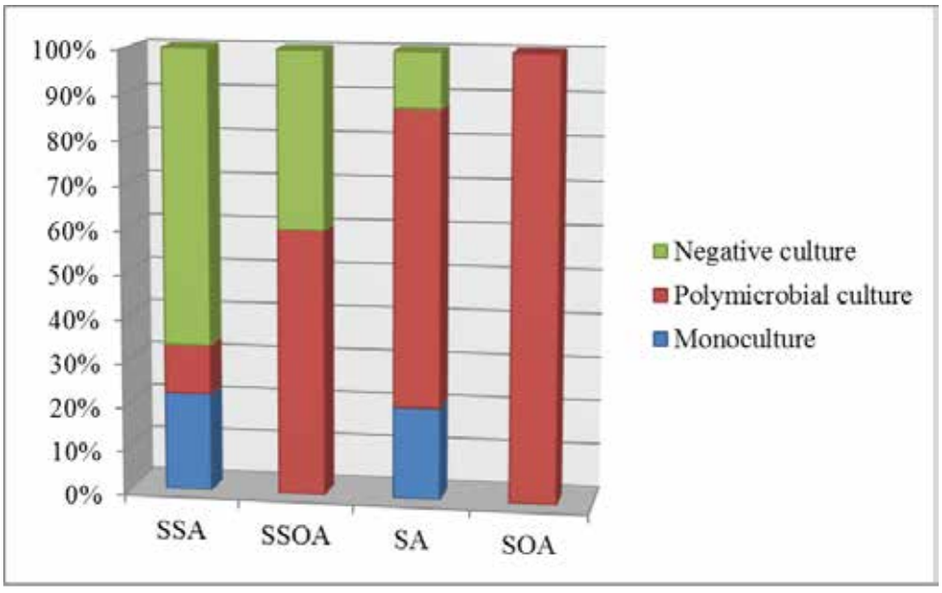
By reviewing the results of patients with SOA and SSOA, it is noticeable that suppurative microorganisms occurred only in mixed infections. This occurred in 100% of patients with SOA and in 60% of SSOA patients. In 40% of patients with SOA the cultures were negatives.

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	Negativecul-ture	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 4: Results of microbiological examinations for each group (n=54).

Septic arthritis			
Phase	**Microorganisms**	**Phase**	**Microorganisms**
Acute	*Staphylococcus aureus* *Streptococcus pyogenes* *Streptococcus agalactiae* *Pseudomonas aeruginosa* *Escherichia coli*	**Chronic**	*Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus agalactiae* *Pseudomonas aeruginosa* *Candida albicans* *Candida So1pp.* *Proteus vulgaris* *Escherichia coli*
Steroid Septic arthritis			
Acute (time after injec-tion of steroids < 2 weeks)	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	**Chronic** (time after injec-tion of steroids > 2 weeks)	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa* *Candida albicans* *Proteus vulgaris*

Table 5: Frequency of incidence of microorganisms according to the phase of the disease.



Diag. 2: Results of bacteriological examinations on groups.

Microorganisms			Staphylococcus aureus (n=3)			Staphylococcus epidermidis (n=4)			Pseudomonas aeruginosa (n=2)		
Antibiotics			R	S	I	R	S	I	R	S	I
Penicillins	Ampicillin		3			2		1	2		
		%	100			50		25	100		
	Bactamed		1		2	1	1	2	2		
		%	33		67	25	25	50	100		
Cephalosporins	Cefazolin			1	2		1	3	1		1
		%		33	67		25	75	50		50
	Ceftriaxone			2	1		2	1			2
		%		67	33		50	25			100
	Cefotaxime			2	1		2	2	1		1
		%		67	33		50	50	50		50
	Cefepime			1	2		1	3			2
		%		33	67		25	75			100
Carbapenems	Meropenem			3			4			2	
		%		100			100			100	
	İmipenem			3			4			2	
		%		100			100			100	
Macrolides	Erythromycin		3			4			2		
		%	100			100			100		
Aminoglycosides	Gentamicin				3	1		3	1		1
		%			100	25		75	50		50
	Streptomycin				3	2		2	2		
		%			100	50		50	100		
	Amikacin			1	2		1	3			2
		%		33	67		25	75			50
Quinolones (Fluoroquinolones)	Ciprofloxacin			1	2		1	2			2
		%		33	67		25	50			100
	Ofloxacin			2	1		1	3		1	1
		%		67	33		25	75		50	50
	Levofloxacin			3			2	2		1	1
		%		100			50	50		50	50
Glycopeptides	Vancomycin			1	2		1	2	1		1
		%		33	67		25	50	50		50

Table 6: Microorganisms sensitivity to antibiotics in patients with SSA. (R - resistant, S - sensitive, I – intermediate).

ANTIMICROBIAL SUSCEPTIBILITY

The study of the obtained strains of microorganisms for their sensitivity to antibiotics in patients with SSA showed a very high sensitivity to Carbapenems and very low sensitivity to aminoglycosides (Tab. 6).

Also microorganisms obtained in patients with SA showed a high sensitivity to Carbapenems. (Tab. 7).

Regarding Quinolones, a similar sensitivity in both groups was observed. Interestingly, an increased rate of Staphylococci vancomycin intermediates in both groups were also observed. In some patients, various fungi such as Candida albicans and Candida spp. have been obtained in polymicrobial associations. However, their analyzes, in particular by types of fungi and their sensitivity to various antifungal drugs, did not reveal a significant difference between different groups of patients.

DISCUSSION

J.H. Newman, 1976 [17] proposed to diagnose septic arthritis according to several criteria. We have included in our research all cases of knee septic arthritis as well as the reasons of the disease. We then introduced the concept of septic osteoarthritis (SOA) with the involvement of cortical

Microorganisms			Staphylococcus aureus (n=22)			Staphylococcus epidermidis (n=10)			Pseudomonas aeruginosa (n=7)			Escherichia coli (n=6)		
Antibiotics			R	S	I	R	S	I	R	S	I	R	S	I
Penicillins	Ampicillin		12		2	4		2	7			6		
		%	55		9	40		20	100			100		
	Bactamed		7	6	8	2	2	6	6		1	3		1
		%	32	27	36	20	20	60	86		14	50		17
Cephalosporins	Cefazolin		4	6	12	2	3	4	5		2			6
		%	18	27	55	20	30	40	72		28			100
	Ceftriaxone		1	12	9		6	4	1	1	5		6	
		%	5	54	41		60	40	14	14	72		100	
	Cefotaxime		1	13	8	1	4	5	5	1	1		5	1
		%	5	59	36	10	40	50	72	14	14		83	17
	Cefepime		2	7	13	2	3	5	2	1	4		5	1
		%	9	32	59	20	30	50	28	14	58		83	17
Carbapenems	Meropenem			20	2		9	1		7			4	2
		%		91	9		90	10		100			67	33
	İmipenem			19	3		8	2		6	1		4	2
		%		86	14		80	20		86	14		67	33
Macrolides	Erythromycin		17		3	9		1	6			6		
		%	77		14	90		10	86			100		
Aminoglycosides	Gentamicin		3	4	15	3	3	4	4		1		3	3
		%	14	18	68	30	30	40	58		14		50	50
	Streptomycin		4	1	16	3	1	6	5		1			5
		%	18	5	77	30	10	60	72		14			83
	Amikacin		2	5	15	2	3	4	2	3	2		4	1
		%	9	23	68	20	30	40	28	44	28		67	17
Quinolones (Fluoroquinolones)	Ciprofloxacin		1	9	12	2	2	6	3	1	2		5	1
		%	5	41	54	20	20	60	44	14	28		83	17
	Ofloxacin		1	12	9	1	3	6	3	1	2		3	3
		%	5	54	41	10	30	60	44	14	28		50	50
	Levofloxacin			13	9		4	6	1	4	1		6	
		%		59	41		40	60	14	58	14		100	
Glycopeptides	Vancomycin			5	13		1	9	5		2			5
		%		23	59		10	90	72		28			83

Table 7: The sensitivity to antibiotics in patients with SA (R - resistant, S - sensitive, I – intermediate).

and subcortical bone tissue, which wasn't previously considered by J.H.Neumann. Upon receipt of a negative microbiological result (11/54, 20.4%), for the diagnosis of SA, we, unlike J.H. Neumann [17] and Chao-Ming Chen et al. 2013 [19], proposed to additionally use as a criterion the data of CRP, ESR and white blood cell count. Only 43 of 54 patients (79.6%) had a positive culture. Monomicrobial infection was observed in 12 patients (22.2%). Polymicrobial infection was observed in 31 patients (57.4%).

Gram-positive bacteria are the most common isolates in septic knee arthritis [4,5,10,19,20-25,21,26]. Despite the presence of various microorganisms, Staphylococcus aureus was in general the most frequent isolated strain. Also in SA patients, gram-positive bacteria played a major role, especially the Staphylococci (45.4%) and Staphylococcus aureus (mean, 29.1%; range, 19-68.9%) was the first. Our findings are in line with a publication, that Staphylococcus aureus represents the main responsible etiological agents in SA. Similar results were observed by many authors [4,10,22-25, 26] for Staphylococcus epidermidis (16.3% vs 12-40%) of literature data. The results of the present study concur with these reports; even in multi-pathogen knee infections, Staphylococcus aureus was in general the most common bacterial isolate.

Positive cultures were observed in the majority (90.3%) of the patients with septic knee arthritis without bone involvement, in line with previous reports by Camilo et al. (91.8%) [5], Chao-Ming et al. (85.9%) [19], and Zar et al. (73%) [21].

By reviewing the results of the patients with SOA and SSOA, it is noticeable that suppurative microorganisms occurred only in multi-pathogen infections. This occurred in all patients with SOA and in 60% of the patients with SSOA (percentages are given for each group). In 40% of the patients with SSOA and in 66.7% of the patients with SSA the cultures were negative (Diag.2). We have not yet been able to interpret these results. We hope that further research will help answer to this question.

There are conflicting reports with respect to the incidence of septic knee arthritis after intra-articular steroid injections [19,27]. Chao-Ming Chen et al. [19], reported that the results of the treatment of SSA did not differ from the results of the treatment of SA with non-steroidal etiology. The authors made these conclusions on a small number of patients. On the other hand Choudhry M.N. et al. [27], reported that the administration of steroid drugs to the joint highly increases sugar in few hours in diabetic patients. According to our data, the difference in microbiological parameters between SA and SSA was expressed only in a higher percentage of negative tests in patients with SSA. Thus, it becomes obvious that it is necessary to continue the study of the effect of steroid drugs on the occurrence of SA, on the microflora and treatment results in more patients.

The ability of Staphylococcus aureus to create pyogenic arthritis as monomicrobial agent is already noted in the literature. This is in contrast with our study, which reports S.epidermidis as the main aetiological agent in monomicrobial infections. Similar results were observed in the early complications after arthroplasty [26,28]. As gram-negatives Pseudomonas aeruginosa was present in mono and in polimicrobial infections. Similar results were obtained in literature [29,30]

Regarding the sensitivity of the 86 isolated strains from all patients, it should be noted that the gram-positive microorganisms were resistant to several antibiotics. These results are confirmed by many studies [31,32,33]. The results of our studies show that polymicrobial microflora is very common in patients with SA. The frequency of polymicrobial microflora especially increases in patients with SOA. In patients with SSA, negative microbiological tests are very common. These features should be taken into account when prescribing antibiotic therapy in patients with knee SA.

CONCLUSION

The results of the bacteriological examinations prove that SA of the knee joint is clinically severe. Besides this, conducting the microbiological analysis in these patients considered a part of the comprehensive examination. Thus, clinicians, prior to receiving the results of microbiological data, may include antibiotics in complex treatment, based on the data obtained. ■

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