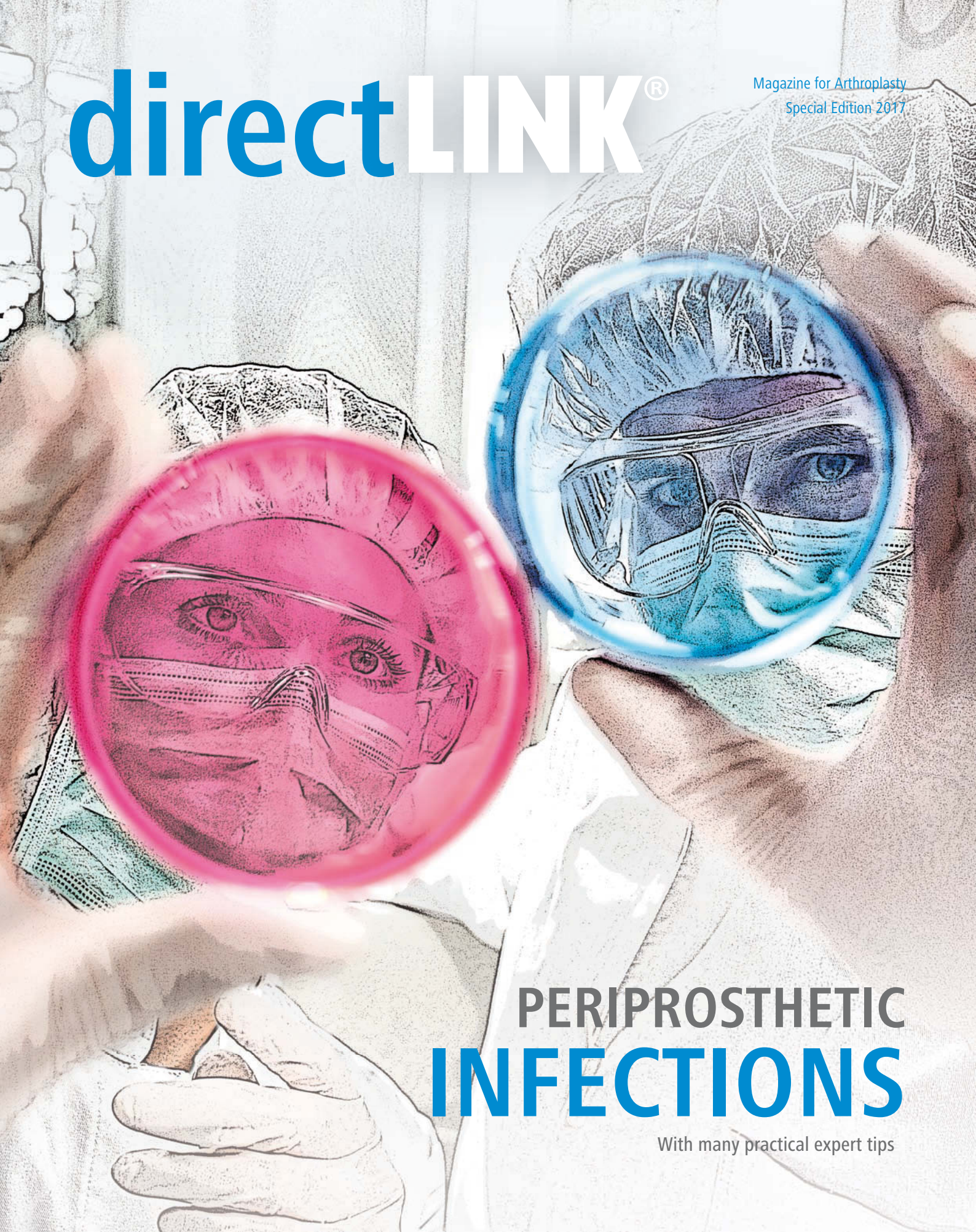
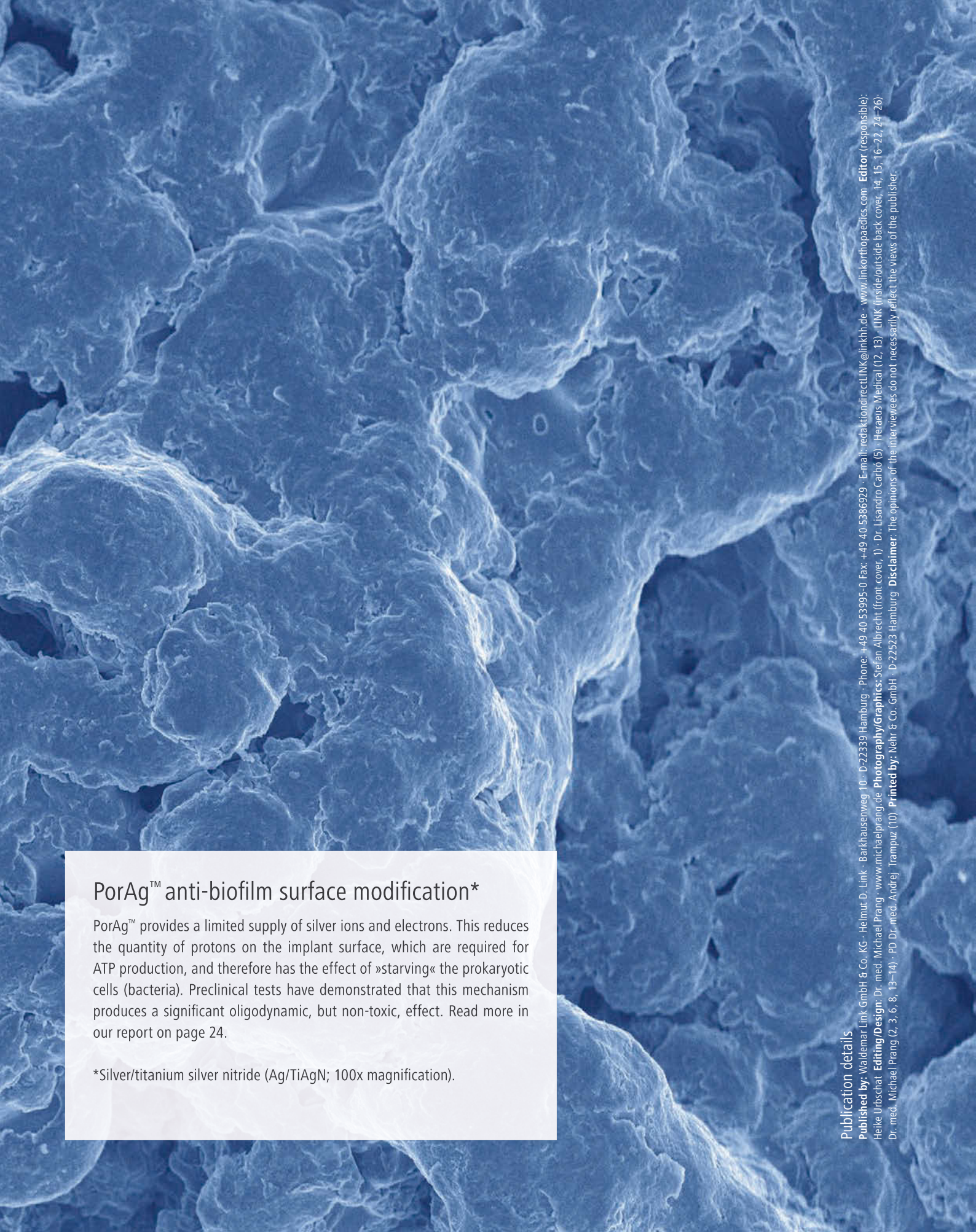
directLINK®

Magazine for Arthroplasty
Special Edition 2017



PERIPROSTHETIC INFECTIONS

With many practical expert tips



PorAg™ anti-biofilm surface modification*

PorAg™ provides a limited supply of silver ions and electrons. This reduces the quantity of protons on the implant surface, which are required for ATP production, and therefore has the effect of »starving« the prokaryotic cells (bacteria). Preclinical tests have demonstrated that this mechanism produces a significant oligodynamic, but non-toxic, effect. Read more in our report on page 24.

*Silver/titanium silver nitride (Ag/TiAgN; 100x magnification).

Publication details

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Dear Readers:

Cases of periprosthetic infection will continue to increase in coming years, according to many experts. Consequently, microbiologists, orthopedic surgeons and traumatologists need answers to three decisive questions here and now. How can periprosthetic infections be avoided? How can they be reliably diagnosed at an early stage? What surgical strategies can be employed to treat patients effectively while preserving their quality of life?

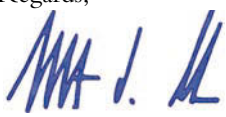
We asked leading experts to come up with answers to these and other important questions, and to give practical tips on how to combat infection. Read the highly interesting and multifaceted responses in this special issue of direct**LINK.**

As manufacturers of high-quality prosthetic joints, and with a major commitment to R & D, we aim to make our own contribution to solving this problem. LINK has a complete product portfolio specifically for revision arthroplasty. In this magazine you will find an overview of our related products, including those specially designed to solve revision problems.

Over the next few years, we shall be bringing further interesting products to market, which can also be used in cases of periprosthetic infection. It is very regrettable, for both patients and surgeons that bureaucratic hurdles sometimes put the brakes on our endeavors to provide the best implants for patients' well-being. Our PorAg™ surface modification, for example, delivers proven benefits for infection prophylaxis and, what's more, there is convincing *Real-world data* to back up this claim. But unfortunately, LINK products with PorAg™ are currently only available as customized solutions.

I hope you enjoy reading this issue of direct**LINK**

Regards,



Helmut D. Link

»We need more government support for our research!«

What has changed since the »International Consensus Meeting on Periprosthetic Joint Infections« in 2013? What needs to be done? A conversation with the initiators, Prof. Dr. med. Thorsten Gehrke and Prof. Dr. Javad Parvizi, MD.

IN THE INTERVIEW

Dr. Javad Parvizi, MD, is professor at the Department of Orthopaedic Surgery at Jefferson Medical College and Thomas Jefferson University in Philadelphia, USA. He is also Vice Chairman of Research and Director at the Rothman Institute, at Jefferson.

Prof. Dr. med. Thorsten Gehrke is Medical Director and Leading Chief Physician in Joint Surgery of the HELIOS ENDO-Klinik in Hamburg, Germany.

Professor Gehrke, Professor Parvizi, in 2013 you initiated the International Consensus Meeting on Periprosthetic Joint Infections (ICM), in Philadelphia, which stimulated a noticeable momentum for the subject. Have there been new findings since?

Prof. Parvizi The ICM was conceived to bring standardization into the management of periprosthetic joint infections. It accomplished three things. It brought together a huge group of people from many countries around the world to agree on the things that we needed to agree and disagree on. This led us to identify areas where we have little evidence for what we do, and so we can seek to generate evidence moving forward. It also brought standardization to protocols, such as definition of periprosthetic joint infection and antibiotic prophylaxis, which used to vary from country to country. We agreed on a vast number of areas in which we need to research in an attempt to generate evidence. Up to 31 randomized prospective studies, which were highlighted by the ICM, have been conducted since.

»One-stage versus two-stage exchange is the next major issue to be addressed.«

Prof. Dr. med. Thorsten Gehrke

On their way back to the airport after the interview: Prof. Javad Parvizi and Prof. Gehrke

Has it been possible to finalize the studies yet?

Prof. Parvizi Yes, one of the questions was, for example, whether to administer antibiotics after re-implantation following a two-stage exchange. My impression at the time was that you don't need antibiotics after implantation if your culture results are negative. However, a randomized prospective multi-center study showed that if you keep these patients on oral suppressant therapy, their failure rate is lower, 5% versus 20%. Another topic that we discussed was the need for inside scraping. All 31 studies have been done as level one randomized prospective studies, with a placebo control whenever appropriate. Those studies, and a few more that will come out this year, will be incorporated into the consensus document in 2018.

Prof. Gehrke We did numerous other studies, for example a randomized study on the Leukocyte Esterase Test, which produced fantastic results. So now we can say that this is quite a good diagnostic tool for periprosthetic joint infections. Of course, there are still many open questions and cut-offs, for example regarding cell cultures. However, there have been many studies published during the last three years which look quite promising.

What are the next major issues that need to be addressed?

Prof. Gehrke One-stage versus two-stage exchange. The group in the Consensus Meeting felt that it was absolutely essential to do a randomized prospective study on that subject. The governing and funding bodies also felt that it was necessary. So, fortunately, two grants in the UK and USA have been issued. Although, we're having issues with the involvement and recruitment of patients. We will eventually finish those studies, which will answer two questions. One is whether one-stage exchange in a properly selected patient group has the same outcome as two-stage exchange? The second, and more important, question is how does one identify patients who are ideal candidates for one-stage versus two-stage exchange?

Prof. Parvizi The other issue that our tumor colleagues face – infection treatment for tumor patients – is an extremely difficult situation. Fortunately, our oncology colleagues felt that there was a need to generate evidence, and they have done two randomized prospective studies that I'm aware of, including one regarding antibiotic prophylaxis in these patients. In our International Consensus Meeting in 2018, we will have separate workgroups, with one workgroup dedicated to oncology.

How is the situation concerning reliable data on PJI's in the US?

Prof. Parvizi The data that has come out of registry databases and administrative databases in the US is not very reliable. The Medicare database did not create adverse questions related to infection. Any study that comes out of the Medicare database has limitations, and that data should not be over-interpreted. The only reliable source of data we have in the US is institutional databases – high-volume centers in the US that do infection work and have built huge databases. At my institution, we now have data on over 6,000 infected joints, with very strict data that has been collected preoperatively and postoperatively. There are other centers that have the same number or more, such as the Mayo Clinic and other high-volume centers. It is very interesting that since the Consensus Meeting, CDC[1] have completed their SSI[2] prevention guideline and given a huge weight of authority and acceptance to the consensus we achieved. They have adopted the definition proposed by the ICM as the CDC's definition of infection.

Prof. Gehrke In Europe, we have the Scandinavian and the UK registries. Unfortunately, we don't have much data from Germany yet. I'm a strong believer in registries. We just inferred that the Swedish

[1] CDC = Centers for Disease Control and Prevention
[2] SSI = Surgical Site Infections

»LINK is a company that really pays attention to periprosthetic joint infections«

Prof. Dr. Javad Parvizi, MD

registry would provide really brilliant data about the outcome and the underestimation of periprosthetic joint infection. However, even in the Swedish registry, the data is not valuable since it was discovered that it overlooked a lot of infections.

What do you think about silver coatings for the prevention of biofilm in light of the waning effectiveness of existing antibiotics?

Prof. Parvizi We've had interest in generating an antimicrobial surface going all the way back to 2003. I wrote my first publication on antimicrobial surfaces. Silver has been around for a very long time and has an antimicrobial property. However, silver is also cytotoxic. If you apply silver in a large enough quantity and on a surface of an uncemented implant, this could compromise the situation. So, finding the right balance, i.e. giving it antimicrobial properties without compromising our situation, is a challenge. I do agree with the principle that we should be looking for an antimicrobial that is not an antibiotic.

Prof. Gehrke I have been in the joint replacement business for 25 years now, and from when I started, antibiotic preparation of the stem was a topic of scientific interest. However, during the last 25 years, I have seen many attempts to cover or coat the stem with antibiotics but there is no definite solution yet. I agree completely with Dr. Parvizi that we need antibiotic-independent material for coating. Silver, like in PorAg™ from LINK, is probably one of the best methods for coating an implant. However, there's still the open question of cytotoxicity.

Prof. Parvizi In the US, the FDA admits that they have no real policy regarding how antimicrobial implants should be approved and brought to market. They are working towards addressing that issue. I think moving into the future, and as infection becomes more and more of a problem, the FDA will change their policies to allow for introduction of antimicrobials that have an anti-colonization property, and perhaps are given an anti-colonization label – at least for the high-risk group. Then we can decide on who the high risk groups are and expand it.

Six tips for combating infection

from Prof. Dr. med. Thorsten Gehrke and Prof. Dr. Javad Parvizi, MD

- **Optimization of the patient:** Don't operate on patients who have issues such as uncontrolled diabetes, active infection in their oral cavities, or patients who are at risk of bleeding, as they're going to require a blood transfusion.
- **Pay great attention to operation room traffic:** Make sure there are not too many people coming and going because they're a potential source of bacterial infection.
- **Do expeditious and safe surgery:** Conserve blood in the operating room and reduce blood loss. Give the patient tranexamic acid treatment or prevent excessive blood loss.
- **Handle the soft tissue gently:** An aggressive approach leaves a lot of dead tissue behind that will then harbor bacteria.
- **Deal very aggressively with the wound related issues in the post-operative period:** Don't assume that persistent drainage from the wound is going to go away by itself. If there's massive hematoma, evacuate it soon.
- **Do a preoperative washing:** In the evening or morning before the surgery, do a washing with chlorhexidine or betadine.

What would you ask governing bodies, surgeons or manufacturers to put more focus on in the future?

Prof. Gehrke We need more government support for our research. They must put more money and energy into this field. I am sure they are going to do that because it's becoming more and more of a general and economic issue. It is, at least, my wish that we receive more government money to create events like the International Consensus Meeting, for example. This is really important. We got great support last time for the International Consensus in 2013 from LINK, which is not the biggest company in this field. That was extremely generous.

Prof. Parvizi I totally agree with Prof. Gehrke. LINK needs to be commended for their very generous financial support at the last ICM. More importantly, I have been following the progress this company has made in this field and they have my admiration. They are a company that understands the importance of paying attention to infection. I hope others follow, because it is important for the industry to recognize it as a problem. Once they do, and throw their weight and money behind it to come up with innovations, that will help us. We are here to work with them, as are all our researchers.

Professor Gehrke, Professor Parvizi, thank you for the interview.

»We Argentinians have to make double the effort!«

Dr. Carbó, you are one of the first surgeons in Argentina to perform single-stage revision in cases of periprosthetic knee infection. Why is that?

I became familiar with the concept in 2013 during my period as a visiting surgeon at the HELIOS ENDO-Klinik in Hamburg, Germany. We are the first to implement the technique successfully in Argentina, and we shall soon be presenting our first results.

In 99.9 percent of cases of periprosthetic infection in Argentina, two-stage revision is still performed. What is the reason for this?

Many hospitals are not equipped for single-stage revision. Most importantly, there is a shortage of infectious disease specialists, while surgeons lack the special training required to carry out the aggressive debridement, for example. Our center receives more referrals of patients with periprosthetic infection than any other in Argentina. The fact that we perform twice as many revisions as two years ago shows that action is needed!

What exactly are the difficulties?

More and more surgeons are becoming converted to the concept of single-stage revision, but it will take a long time before it becomes widely established. One reason is that many patients are tied to specific hospitals by their health insurers. The surgeons at these hospitals would actually prefer to perform single-stage revision, but are not in a position to do so.

Are there any other reasons?

We Argentinians have to make double the effort because in addition to a lack of necessary resources, we also have the problem that at many hospitals there is no consensus regarding treatment of periprosthetic infections. We need efficient, recognized concepts in this area. That's why we devote so much attention to this subject at the meetings of the Argentinian Orthopedic and Traumatology Association (AAOT).

LINK has an extensive revision portfolio. Which implants do you use?

For revisions involving infections that demand massive debridement, I use the Endo-Model® Rotational Knee Prosthesis, and if there is a major bone defect, I choose the Megasystem-C®. I shall be using the oligodynamic surface modification of LINK PorAg™ as soon as it becomes available in Argentina.

Dr. Carbó, many thanks for this interview.

Dr. Lisandro Carbó is head of the Knee Department at the Italian Hospital of Buenos Aires, Argentina

»Silver coatings for the prevention of biofilm is a very interesting approach!«

What is the situation in Germany with regard to periprosthetic infections? An interview with Dr. med. Lars Frommelt about data problems, preoperative decontamination and the importance of silver for infection prophylaxis.

Dr. Frommelt, there is no evidence-based data on the diagnosis and treatment of periprosthetic infections for Germany. Why is that?

Because we do not have any controlled studies. For ethical reasons it's not possible to compare single-stage and two-stage procedures. Besides which, many hospitals do not wish to depart from their standardized procedures so as to avoid any deterioration in outcomes. If you have a 90 percent success rate with a particular surgical procedure, you don't want to test it against a different procedure with which you may only achieve 80 percent success.

In your estimation as a specialist, how many arthroplasties lead to a periprosthetic infection?

According to the KISS[1] data, around 1.2 percent; the BQS[2] and traumatology data together give a figure of around 1 percent. Most infections result from intraoperative contamination, although the clinical symptoms only appear 18 months later, on average. Propionibacteria, as typical pathogens of low-grade infections, can even cause an infection after five years. The data does not help us because the observation periods are too short. The KISS data, for example, only extends up to hospitalization.

What preoperative measures against hematogenous infections do you recommend?

Conventional antibiotic prophylaxis is already applied; preoperative general infection screening plus treatment of any dental, ENT and urological infections are becoming increasingly established, ideally on an outpatient basis. A new measure is preoperative washing with disinfectants, which should be performed until the wound has healed completely.

AN INTERVIEW WITH

Dr. med. Lars Frommelt is an infectious disease specialist and clinical microbiologist. He is in charge of the bone database at the Institute of Infectiology, Clinical Microbiology and Hospital Hygiene at the HELIOS ENDO-Klinik, Hamburg, Germany.

What action should be taken if a periprosthetic infection is suspected?

The key factor is the diagnosis. 20 percent of infections have no visible symptoms. This raises the possibility of a periprosthetic joint infection being mistaken for loosening with other causes. The Philadelphia Consensus identified principal criteria such as double detection of identical pathogens and a fistula. Secondary criteria are, for example, leukocyte differentiation and detection of bacteria. So there are criteria by which an infection can be judged likely or unlikely. And these criteria must be applied systematically.

What should be the guiding principle for the therapeutic procedure?

In the event of an acute, early symptomatic infection, it may be possible to preserve the prosthesis within three weeks by means of surgery and antibiotics. But only if one acts swiftly. If the time window is missed, it means complete replacement of the prosthesis because the joint space poses no barrier for bacteria. Whether the single-stage or two-stage procedure is adopted is of no importance in microbiological terms. Two-stage exchange can make a lot of sense if the pathogen has not been identified, as this is central to the antibiotic treatment.

Three tips for combating infections

from Dr. med. Lars Frommelt

- Systematic preoperative elimination of infection
- »Appropriate« use of antibiotics with correct dosage for an adequate length of time
- Decontamination from preop through to complete wound healing.

LINK has developed PorAg™, an oligodynamic surface modification designed to prevent biofilm. What is your opinion about PorAg™?

It is a very interesting functional approach. Silver coatings were developed for tumor patients who have an infection risk of around 25 percent due to the combination of polychemotherapy, radiotherapy and surgery. Silver-coated megaprostheses with low toxicity could reduce this risk for tumor patients from 25 to 10 percent.

Silver is regarded as a medicinal product, and therefore authorization of implants with an oligodynamic silver coating is impossible in Germany at the present time.

I regard that as an inappropriate regulation. Antibiotic-impregnated bone cement is an approved medical device, and not a medicinal product, even though its sole purpose is not to protect the cement but to protect the body against infection. This loophole has been closed by the regulators, but bone cement remains authorized for legal reasons.

Dr. Frommelt, many thanks for this interview.

[1] KISS = Hospital Infection Surveillance System.
[2] BQS = BQS Institute for Quality and Patient Safety.

»Silver-coated megaprostheses could reduce the infection risk for tumor patients from 25 to 10 percent.«

Dr. med. Lars Frommelt

»There's a lot you can do right in the fight against infections!«

Periprosthetic infections can be prevented if they are tackled head-on, says PD Dr. med. Andrej Trampuz. An interview about the pillars of diagnostics and therapy.

Dr. Trampuz, you have created algorithms designed to prevent or cure periprosthetic infections. How does the concept work?

Infectious disease specialists alone achieve cure rates of 50 to 60 percent for periprosthetic infections. Surgeons who perform a perfect operation do not manage a higher percentage because often they fail to prescribe the optimal antibiotics. Therefore, our concept essentially consists of a differentiated diagnosis with the aim of identifying the pathogen. Surgeons, infectious disease specialists and microbiologists work together to optimize the diagnostics, surgery and use of antibiotics.

On what data are the algorithms based?

We utilize a database of patient data from Switzerland, where I worked for 15 years. It contains data from 5,000 patients whom we examined in a follow-up after two, three, five and ten years. For 25 years now, we have been working on concepts for preventing or curing periprosthetic infections. Following in-vitro tests, we developed an animal model that reflects the situation of human patients very closely. In this way we have tested almost all new antibiotics and also diagnostic and preventive methods. So we have very good knowledge about the success rate of each procedure.

»The true incidence of periprosthetic infections is probably around 5 to 10 percent.«

PD. Dr. med. Andrej Trampuz

AN INTERVIEW WITH

Internist and infectious disease specialist **PD Dr. med. Andrej Trampuz** is chief physician at the Center for Musculoskeletal Surgery in the Orthopedic Department of the Charité Universitätsmedizin Berlin, Campus Mitte, Germany, and head of Infectiology and Septic Surgery. His clinical and scientific specialty is periprosthetic infections.

What does your data show?

The data shows that over 90 percent of patients treated according to our algorithms no longer suffer any periprosthetic infections. The treatment periods are considerably shorter, usually two to three weeks of hospitalization, which makes the experience less stressful and less costly. That's very good news for patients because it means we can treat virtually any infection, and send the patient to rehab or back home with a pain-free and fully functional joint.

You have presented your concept in a six-page Pocket Guide, and also as an app, in six languages. Who uses the Pocket Guide?

Both experienced surgeons and younger colleagues: currently we have up to 30 downloads per day worldwide. On the website of our Pro-Implant Foundation[1], we offer workshops in which we explain the concept. The Pocket Guide is updated every three months.

You are also working on a European database.

Yes, we aim to launch it in several countries in 2017 and involve all the major hospitals so that we can collate around 5,000 patients in the space of two years. The database illustrates the entire treatment, including which prosthesis was used and whether cemented or cementless. We then examine which factors are associated with the greatest success, and what sorts of failure occurred, and why. The findings are immediately incorporated into our algorithms. The aim of the Epjic Project[2] is to obtain valid data beyond double-blind randomized prospective studies. In addition, we carry out prospective studies in which we randomize and systematically analyze patients, and try out new tests and antibiotics.

Many pre-, intra- and postoperative measures for avoiding infections are well known but not systematically implemented.

It's essential to be rigorous in establishing the cause of infections. For example, in the case of one patient, perfect diagnostics were carried out and the propionibacterium was identified. A single-stage revision was performed and the new joint prosthesis implanted with cement. But in the final analysis, the intervention was not successful because the patient was only given a two-week course of antibiotics instead of the six weeks required. Now, a few months later, the patient has returned with pain.

Are there any new developments in infection prophylaxis?

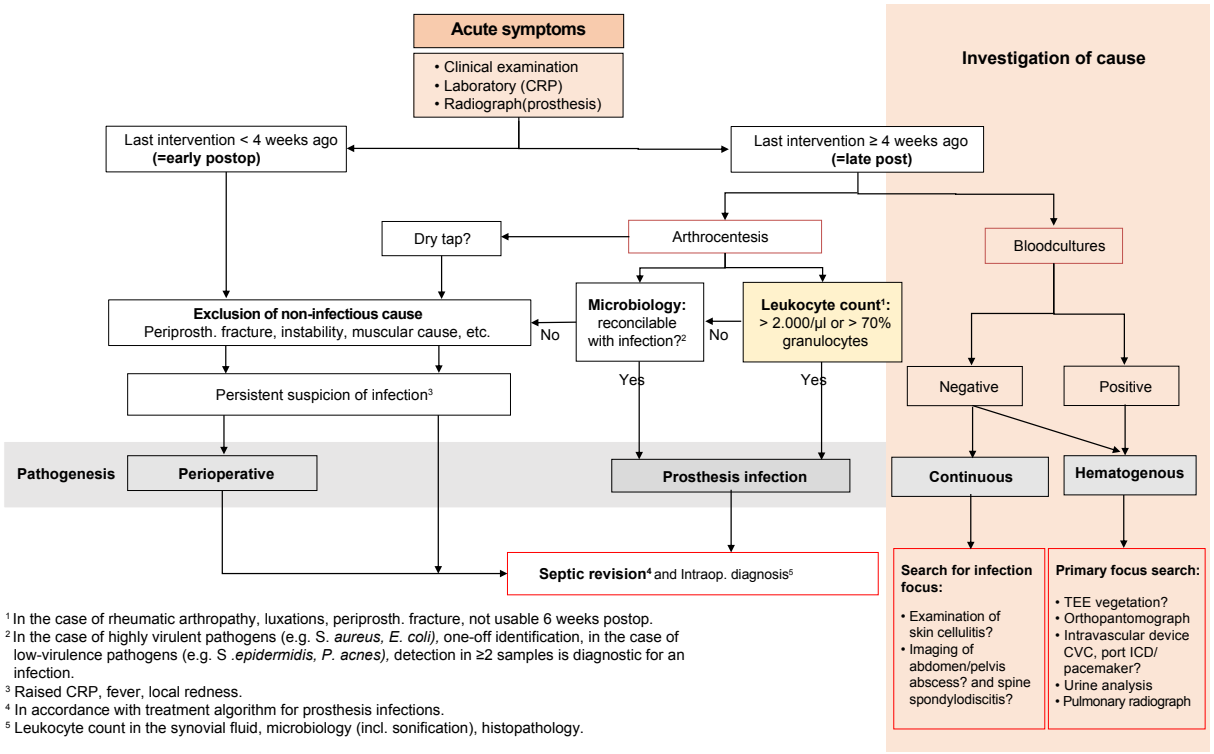
Yes, with spine patients, and soon with prosthetic joint patients, we are conducing a multi-center postoperative study with a vaccine against staphylococcal infections. 10 to 60 days before the planned operation,

Five tips for combating infection

from Dr. med. Andrej Trampuz

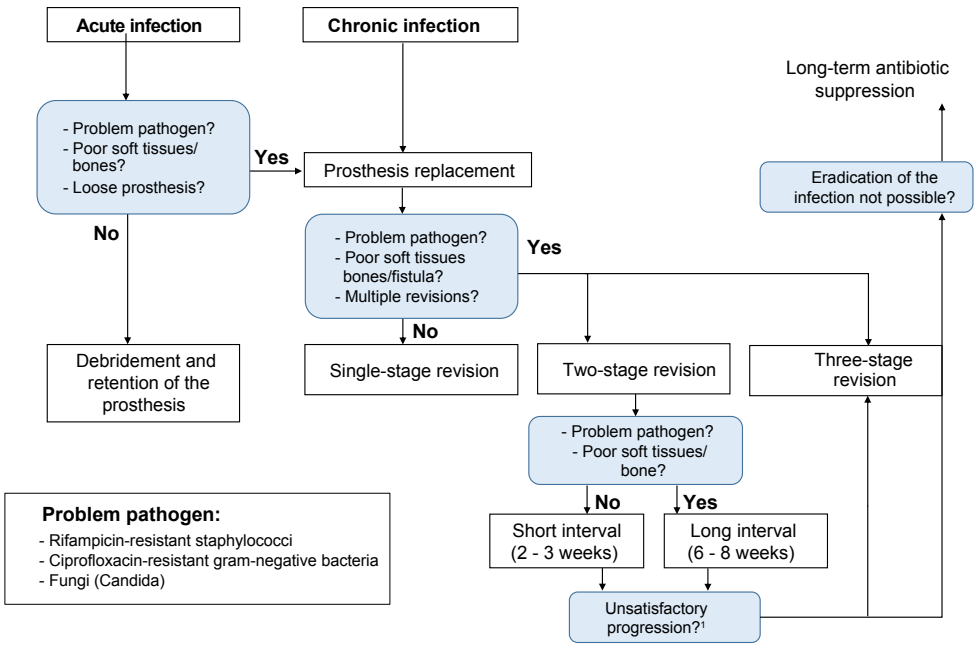
- Preoperative washing of the entire body with antiseptic soap
- Perioperative antibiotic prophylaxis 30 to 60 minutes before the surgical incision
- Arthrocentesis if periprosthetic infection is suspected (for example, pain, prosthetic loosening)
- The leukocyte count in the synovial fluid is key to diagnosing the presence of infection
- Taking of blood cultures from febrile patients to exclude the possibility of hematogenous periprosthetic infections

DIAGNOSTIC ALGORITHM



[1] In the case of rheumatic arthropathy, luxations, periprosth. fracture, not usable 6 weeks postop.
[2] In the case of highly virulent pathogens (e.g. S. *aureus, E. coli),* one-off identification, in the case of low-virulence pathogens (e.g. S .*epidermidis, P. acnes),* detection in ≥2 samples is diagnostic for an infection.
[3] Raised CRP, fever, local redness.
[4] In accordance with treatment algorithm for prosthesis infections.
[5] Leukocyte count in the synovial fluid, microbiology (incl. sonification), histopathology.

TREATMENT ALGORITHM



[1] Clinical signs of infection, raised CRP, pus (intraoperatively), compromised soft tissues

The future for revisions lies in functionalized surfaces with antimicrobial properties.

PD Dr. med. Andrej Trampuz

the patients are given a dose against *Staphylococcus aureus*. Preliminary trials have shown that the S. aureus infection can be prevented in this way in 70 percent of patients. This could be an additional prophylactic approach for the future.

How big a role do the implant surfaces play in infection prophylaxis?

The surface has little influence on the infection risk. Every implant is first coated with endogenous fluid, and most bacteria then colonize this layer. What bacteria particularly like is the rough cement surface, followed by polyethylene and the metals, although there are few differences between these in vivo. In my view, the future for revisions lies in functionalized surfaces with biofilm-inhibiting properties.

Could that mean silver coatings?

Yes, that's one possibility. Alongside systemic antibiotic therapy, which we describe in detail in the Pocket Guide, local biofilm-inhibiting measures will become increasingly important. We see considerably fewer infections with antibiotic-impregnated cement. With local biofilm-inhibiting measures, we're sure to have even more success with revisions.

What does the future to hold in terms of periprosthetic infections?

I can't envisage any horror scenarios. We're constantly improving in our ability to detect problem pathogens and apply suitable therapy. We're already able to cure most infections and achieve good joint function. What we need is new products, a bundle of different preventive measures, and well trained personnel so that every patient can be given optimal treatment from the outset. The objective is to reduce infection rates to well below 1 percent. Currently we are well above that figure.

How can the target to be achieved?

We could achieve the greatest benefit by showing the hospitals how to respond quickly and to perform the primary arthroplasty correctly. If you don't do it correctly, the second operation is far more difficult because, in most cases, the pathogens can no longer be identified, as they have already been exposed to antibiotics once. You can do some things wrongly – but a lot of things right.

Dr. Trampuz, thank you for this interview.

[1] www.pro-implant.foundation.org.
[2] www.epjic.org.

Is bone cement still the gold standard for infection prophylaxis?

What role does antibiotic-impregnated bone cement play in prophylaxis against periprosthetic infections? A visit to Heraeus Medical.

Production of PALACOS® R+G pro at Heraeus Medical

THE COMPANY

Heraeus the technology group, headquartered in Hanau, Germany, was established in 1851. Today, with its combination of materials and technology expertise in the fields of environment, energy, health, mobility and industrial applications, the family-owned business is a world-leader. **Heraeus Medical** specializes in medical devices for surgical orthopedics and traumatology. As the industry leader for bone cements, the company is a multiple winner of the TOP 100 Award as one of the most innovative German SMEs (small and medium-sized enterprises).

»The data from numerous registries and randomized studies demonstrate that antibiotic-impregnated bone cement reduces the number of infection-related revision arthroplasties«, said Dr. André Kobelt, Managing Director of Heraeus Medical. For this reason, bone cement with antibiotics is still regarded as the gold standard for prophylaxis against periprosthetic infections. The criticism, particularly in the USA, that the risk of emerging resistance would increase as a result is unproven.

»In Sweden, where Gentamicin is very widely used, there was no increase in resistance«, stated Dr. André Kobelt. Furthermore, a study conducted at the German HELIOS ENDO-Klinik showed no antibiotic concentrations in the blood or urine, or subfascially which could lead to resistances. »Nevertheless, it's important to know against which microbe the bone cement is being used«, Dr. André Kobelt explained. "Together with our partner *Curetis,* we have developed a PCR-based (polymerase chain reaction) process that allows the predominant microbe and the appropriate antibiotic to be identified within four hours.«

Modern cementing technique maximizes prosthesis life

The fact is that Heraeus Medical is concerned not just with bone cement, but with the complete treatment pathway. Thorough preparation of patients, especially those who are at increased risk of

infection, and expert preparation of the bone bed are the first prerequisite, after which the correct cementing technique represents the next decisive step for ensuring that the prosthetic joint has a long service life. In the course it offers at its *PALACADEMY*, Heraeus recommends the vacuum mixing system because this optimizes the mechanical properties of the cement. »It has been documented that antiquated mixing techniques bring out different mechanical properties, and that implants placed using a modern cementing technique have the longest service lives«, stated Lothar Kiontke, Head of Marketing.

Other important factors for the long-term success of infection prophylaxis are the surface quality and design of the prosthesis. »The bone cement should be tailored to both – it must be neither too elastic nor too rigid if a homogeneous cement mantle is to be achieved«, explained Dr. André Kobelt. »One of the best combinations of implant and cement, according to the Swedish registries, is possible with *PALACOS* from Heraeus and the anatomic Lubinus SP II® stem from LINK.« Especially for revision arthroplasty, the key is always differentiated use of the various cement products and antibiotic mixtures. »We have *COPAL G+V with vancomycin* as a new product on the market«, said Dr. André Kobelt. »This cement definitely should not be used across the board. It is essential to identify the bacterium, as otherwise antibiotic protection of the cement-bone interface will not be achieved, and biofilm-related loosening of the implant becomes likely.«

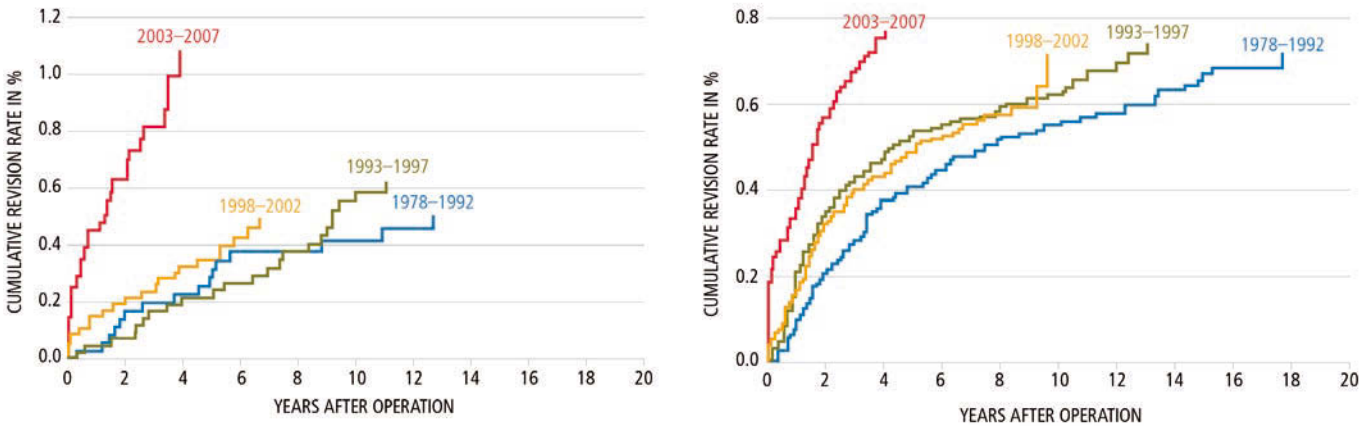
A 10 percent cost saving is possible

If all the components are correct, the optimal cement-antibiotic-prosthesis combination can not only improve the outcome for the patient but also reduce the cost of the treatment. »A randomized study from the UK with over 800 patients, in whom femoral neck fractures were treated with cemented joint prostheses, shows that the use of *COPAL G+C*, a cement with an antibiotic combination, prevents infection in at least three in a hundred hemiarthroplasty patients – and does so without causing any relevant resistances«, according to Dr. Kobelt. »With three cases of infection, this amounts to a ten percent cost saving for all hemiarthroplasties – simply by taking a different pack of bone cement off the shelf!«

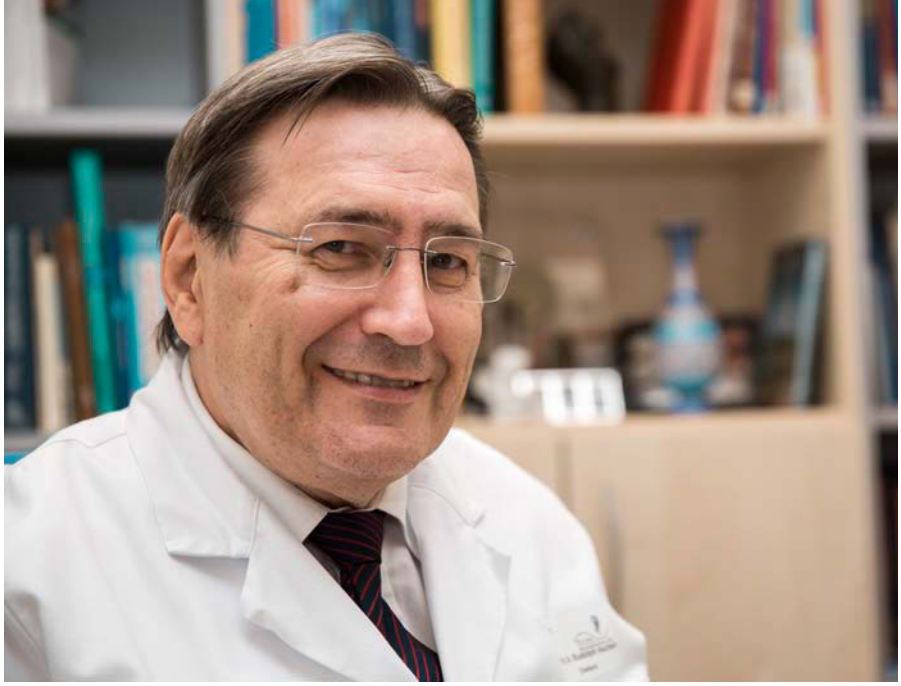
»Studies confirm that antibiotic-impregnated bone cement reduces the number of infection-related revision arthroplasties.«

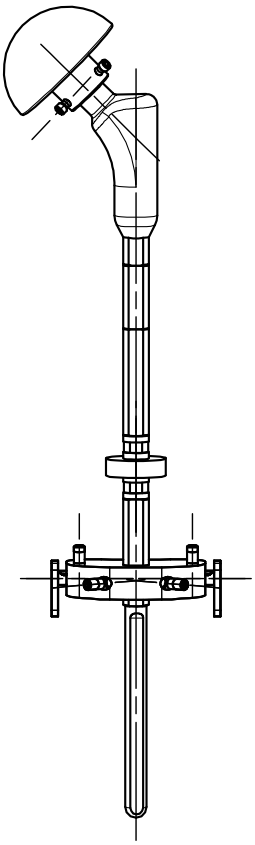
Dr. André Kobelt, Managing Director of Heraeus Medical

Bone cement experts: Head of Marketing Lothar Kiontke, Managing Director Dr. André Kobelt and Head of Marketing Operations Meike Zimni (l. to r.)



Percentage of revisions due to deep infection with cementless (left) and cemented (right) primary knee prostheses over four periods (x-axis: number of years postop, y-axis: cumulative revision rate in percent)





»A postoperative infection is not a treatment error but a new illness!«

Not all arthroplasty challenges can be overcome with conventional antibiotic spacers. An interview with Prof. Dr. med. Rudolf Ascherl about the modular temporary prosthesis which he developed.

Professor Ascherl, you developed a temporary prosthesis, which is currently being produced by LINK as a customized solution. How does it differ from conventional antibiotic spacers?

Our temporary prosthesis is made of implant steel, is uncoated and modular. We can use it to bridge any length, even the entire femur. The leg is then reasonably stable, whether the patient is standing, sitting or being cared for in bed. No special surgical technique is required.

Why are standard spacers not adequate for your purposes?

If, for example, you have to remove a tumor prosthesis, and the patient no longer has any thigh bone, you need a bridge between pelvis and lower leg which meets three important criteria: stability, length and dead space filling. That is not possible with conventional spacers. They are always individual designs with intramedullary nails and tubes from the fixators. We have developed a system that fits precisely and creates a certain stability when (re-)positioning and caring for the patient. Besides which, our system enables us to reduce the size of larger defects because the tissue shrinks around the temporary prosthesis. The hollow spaces are then smaller when it comes to placing a new prosthesis.

How do you achieve adequate antibiotic protection with the uncoated temporary prosthesis?

In difficult cases, we coat the temporary prosthesis with an antibiotic-impregnated collagen film. In addition, depending on

AN INTERVIEW WITH

Prof. Dr. med. Rudolf Ascherl is Medical Director of the Department of Special Surgery and Arthroplasty at Tirschenreuth Hospital, Germany.

the results of the microbial test, we administer systemic antibiotics, generally for no more than four weeks. As these patients usually have multi-resistant microbes as well as difficult soft tissue damage and massive bone infections, we often irrigate and debride multiple times until we achieve a low microbial count or complete sterility.

»With our temporary prosthesis, we can bridge any length, even the entire femur.«

Do you sometimes use antibiotic spacers?

I'm not opposed to antibiotic spacers. But I'm very cautious because of the X-ray contrast medium they contain, the possible fractures and abrasion. Besides, the polymer surface of the spacers could attract microorganisms which form new biofilm.

How many temporary prostheses have you implanted up to now?

So far we have performed around 120 operations, so we will soon be able to make an evaluation. The prosthesis is not intended for wide use, but I believe that we have come up with a quick and easy solution for patients who would otherwise be faced with an amputation. You see, a postoperative infection is not a treatment error, but a new illness. You have to practice prophylaxis and diagnostics – and if an infection should occur, you have to be able to treat it optimally.

Do the legal regulations make it difficult to get these products approved?

There are enormous obstacles to overcome before such urgently needed products can be placed on the market, and that is a major problem. Imagine a young patient has a periprosthetic infection of his tumor prosthesis and needs suitable bridging. In an age where we're capable of making customized prostheses, we should also have implants for such patients.

Professor Ascherl, many thanks for this interview.

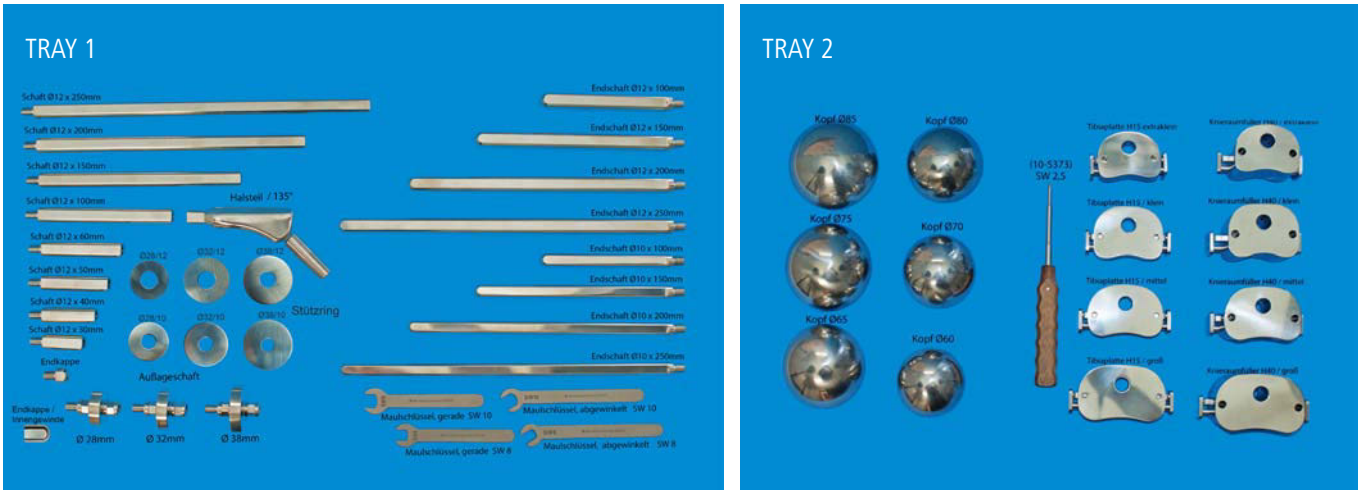
»Stability, length and dead space filling are the three criteria for spacers with which we are concerned.«

Prof. Dr. med. Rudolf Ascherl

Three tips for combating infections

from Prof. Dr. med. Rudolf Ascherl

- Urging the patient at an early stage to take care of their skin – for example, they should avoid scratching
- Giving the patient information and responsibility, especially for reporting any symptoms
- Thorough preoperative inspection of the skin, nose, pharynx, teeth, bladder etc. for infections



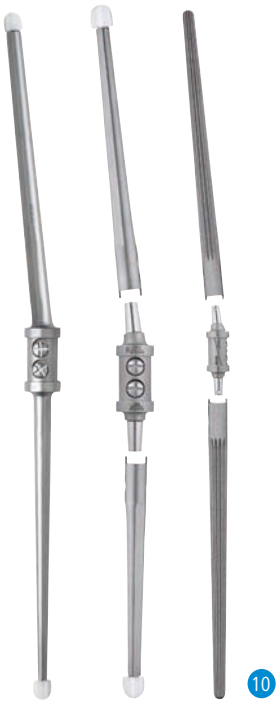
Stability, length and dead space filling: the temporary prosthesis developed by Prof. Ascherl is produced by LINK as a customized solution

Selection from the LINK portfolio for primary and revision arthroplasty

1) LINK® SP II® Lubinus® Anatomic Hip Prosthesis with best outcomes in the Sweden study*
2) LINK® Lubinus Classic Plus® Hip Prosthesis System, the modern standard implant 3) LINK® Standard C Cem Hip Prosthesis, cemented standard stem C 4) LINK® Standard M Hip Prosthesis, cemented hip prosthesis with established concept 5) LINK® Dysplasia Stem, straight-stem prosthesis for cemented implantation

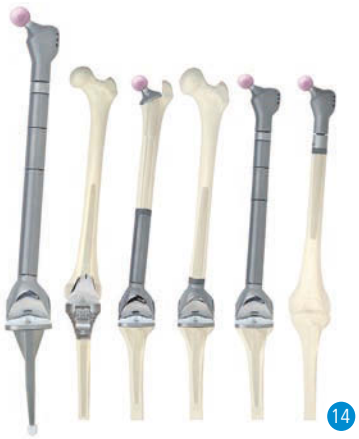
*Annual Report 2013; Swedish Hip Arthroplasty Register; www.shpr.se

6) LINK® Lubinus® Acetabular Cup, cemented, for the LINK® SP II® Hip Prosthesis Stem 7) LINK® IP Acetabular Cup, cemented, for the LINK® SP II® Hip Prosthesis Stem 8) LINK® FC + FAL Acetabular Cup, cemented polyethylene acetablular cup 9) LINK® Endo-Model® Polyethylene Acetabular Cup, cemented acetabular cup in right and left versions

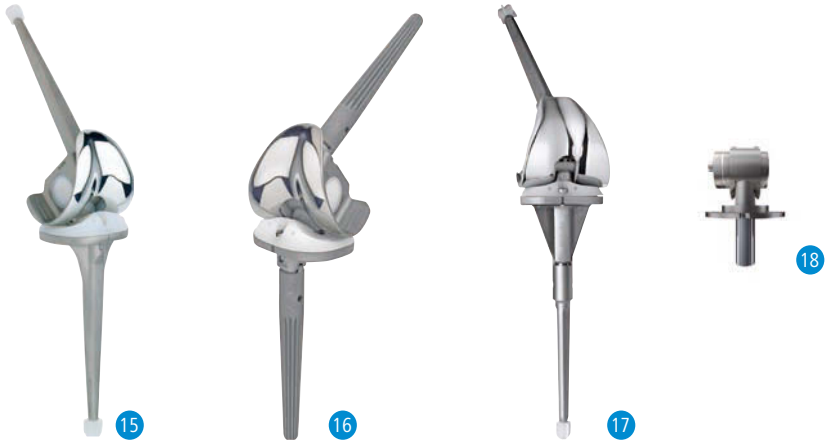


10) LINK® Endo-Model® Knee Fusion Nail SK, modular system for cemented or cementless implantation

11) LINK® SP II® Long Stems, cemented long-shaft prostheses for hip revision (left: anatomic; right: XL version)
12) LINK® Revision stems; straight and anatomic prostheses for hip revision 13) MP® Reconstruction Prosthesis, modular cemented and cementless prosthesis for hip revision



14) LINK® MEGASYSTEM-C®, the modular tumor and revision system



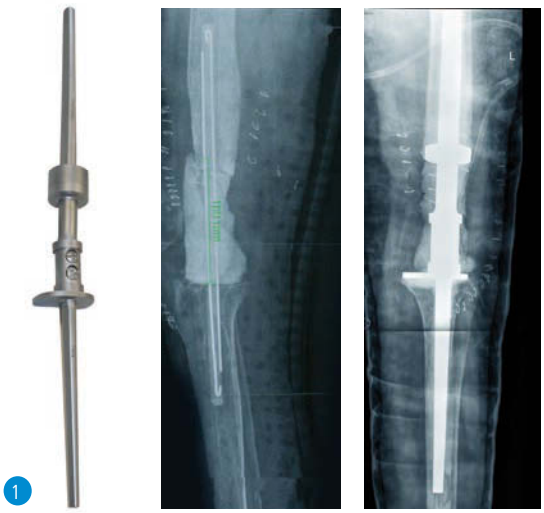
15) LINK® Endo-Model® Rotational and Hinge Knee Prosthesis for primary and revision surgery 16) LINK® Endo-Model®-M, Modular Knee Prosthesis System with segmental bone replacement components 17) LINK® Endo-Model® SL® Rotational and Hinge Knee Prosthesis 18) Arthrodesis Coupling for the LINK® Endo-Model® SL® (with connecting components for rotational and hinge joints)

19) The oligodynamic PorAg™ surface modification for preventing biofilm is available from LINK as a customized solution

20) Interposition sleeves »RescueSleeve™«, for interprosthetic fractures, available as custom-made implants 21) LINK® Partial Pelvis Replacement Endo-Model®, implant for bridging larger bone defects 22) LINK® Pelvis Support Type RR & Type RC acetabular roof support ring and acetabular roof support tray (Type RC bottom image)

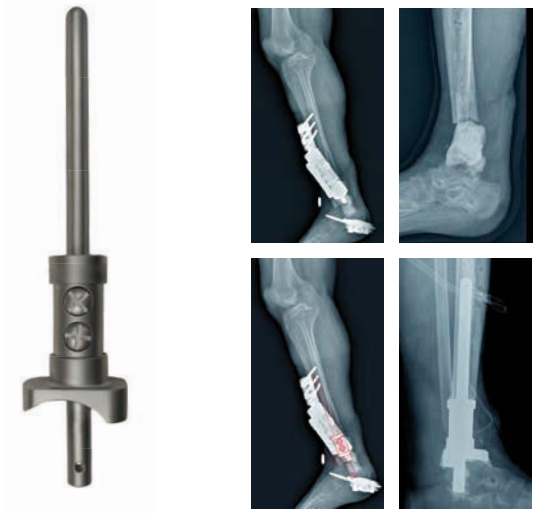
23) Prefabricated, ready-to-use **Link**Spacer with gentamicin for hip and knee replacement

Examples of special customized solutions for prosthetic requirements involving infections



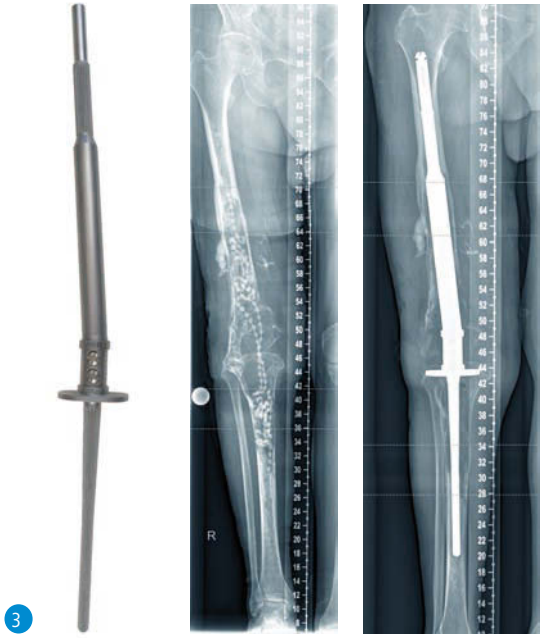
1

Cemented Knee Fusion nail with modular, distal partial femur replacement and anatomically curved stem; left: state after infected knee prosthesis and temporary nail splinting with administration of antibiotics



2

Arthrodesis nail for the ankle; fracture of the tibia and screw fixation with osteosynthesis plates. Due to infection after one year, an external fixator was placed, while the distal tibia was removed and replaced with antibiotic spacers. After removal of the fixator, an arthrodesis nail was implanted with partial tibial replacement and talus support.



3

Cementless arthrodesis nail from LINK; state after arthrodesis of the right knee joint, with state following prosthesis infection and soft tissue flap surgery plus material loosening with reinfection by staphylococci

4

Customized partial pelvis replacement with modified MP® prosthesis from LINK; state after complex infectious damage of the hip with preceding resection of acetabulum and femur; the antibiotic spacer (top radiograph) served as spacer until revision was performed

New: **Link**Spacer with antibiotics

New from LINK for knee and hip replacement: prefabricated, partially cemented spacers with antibiotics for two-stage use in cases of periprosthetic infection. The LinkSpacer can be used as a temporary replacement for a joint prosthesis which has to be removed due to an infection.

Articulating spacers offer many advantages

Many authors consider that, for two-stage revision, the use of articulating spacers has numerous advantages compared to block spacers. For example, the joint cavity is retained, and retraction of the collateral ligaments is prevented. Furthermore, antibiotic-impregnated spacers ensure continuous elusion of local antibiotics.[1] Conventional block spacers, on the other hand, lead to undesirable joint stiffness.[2,3]

Antibiotics increase the effectiveness of spacers

Articulating spacers have a large surface area in contact with the surrounding bone and soft tissue, and they also cover a large intraarticular surface. This results in a correspondingly large exchange surface for the antibiotic contained in the spacers. That increases their effectiveness.[4] The LinkSpacer remains in its position until the soft tissue fully recovers and normal inflammation values are reached.

LinkSpacer **for the hip joint**

- Effective release of gentamicin in situ, highly concentrated local antibiotic treatment
- Metal structure for high resistance to physiological mechanical stress
- Simple implantation
- Prevents tissue retraction and facilitates later revision and reimplantation
- Maintains the functionality of the hip muscles
- Partial loading of the joint is possible if required
- Rapid rehabilitation of the patient because joint mobility is maintained
- Improved quality of life between surgical interventions

The LinkSpacer for the hip joint is equipped with a reinforced core of implant steel (AISI 316L), which is surrounded with gentamicin-containing bone cement. The partially cemented LinkSpaceris available in eight versions.

LinkSpacer **for the knee joint**

- Effective release of gentamicin in situ, highly concentrated local antibiotic treatment
- Joint space is preserved
- Simple access for revision because patellar tendon without cicatrization as a result of immobilization
- The extensor muscles can be preserved by rehabilitation
- Functional secondary ligaments
- Short functional recovery time after final revision procedure
- Better mobility than with block spacer
- Partial loading of the joint is possible if required
- Improved quality of life for the patient

The LinkSpacer for the knee joint corresponds to a congruent condylar knee prosthesis. Six models are available, implemented in acrylic cement impregnated with gentamicin. The LinkSpacer comprises independent tibial and femoral elements.

[1] Walker RH, Schurman DJ (1984) Management of infected total knee arthroplasties. Clin Orthop Relat Res 186:81–89

[2] Haddad FS, Masri BA, Campbell D, McGraw RW, Beauchamp CP, Duncan CP (2000) The PROSTALAC functional spacer in two-stage revision for infected knee replacements. J Bone Jt Surg Br 82:807–812

[3] Meek RM, Masri BA, Dunlop D, Garbuz DS, Greidanus NV, McGraw R, Duncan CP (2003) Patient satisfaction and functional status after treatment of infection at the site of a total knee arthroplasty with use of the PROSTALAC articulatingspacer. J Bone Jt Surg Am 85:1888–1892

[4] Ocguder A. et al: Two-stage total infected knee arthroplasty treatment with articulating cement spacer; Arch Orthop Trauma Surg (2010), 130:719–725

LINK® Endo-Model® Knee Fusion Nail SK for use after infectious revision TKA

Infections after knee joint revision due to preceding periprosthetic infection can be a therapeutic challenge because of the loss of bone substance and soft tissue integrity. In such cases, arthrodesis provides a recognized solution.

The design of the LINK® Endo-Model® Knee Fusion Nail SK combines a high degree of modular flexibility and maximum reliability. Implantation is intuitive and simple, and ensures primary stability, enabling rapid, loadable mobilization.

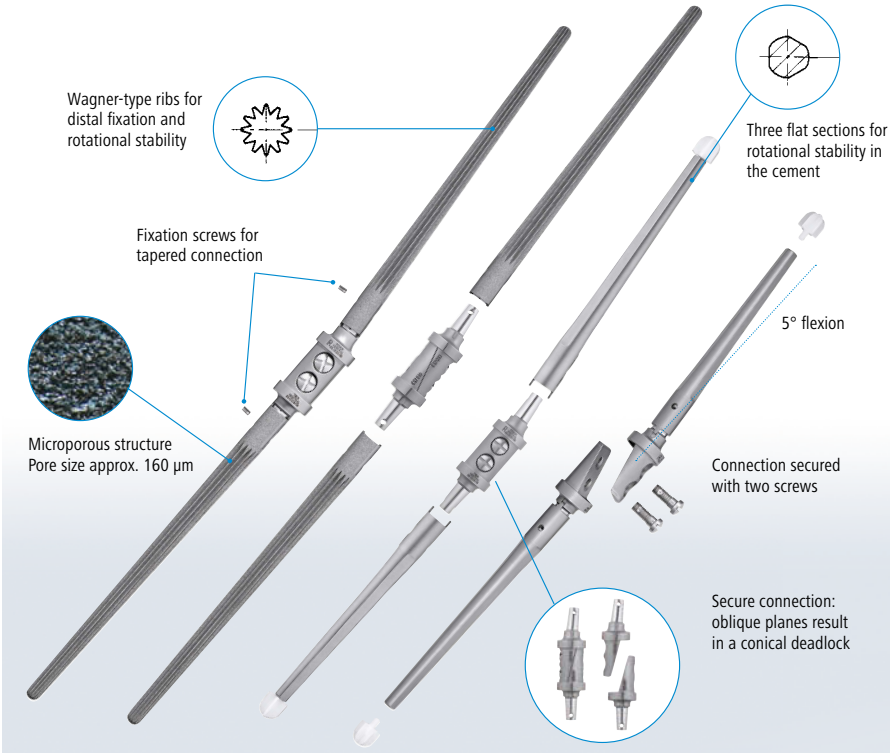
Modular system for cemented or cementless implantation

The cemented Knee Fusion nail is made of an EndoDur® CoCrMo alloy. The modular coupling can be combined with all the modular stems from the LINK® Endo-Model® family which have a female taper, and thus permits cementless implantation with Tilastan® stems and cemented implantation with CoCrMo stems. The oblique coupling plane in the arthrodesis lock and engagement of the components in annular pockets create a frictional connection which is secured with two screws. With the cemented version, the focus must be on secure primary locking in the medullary space – with or without a bone graft.

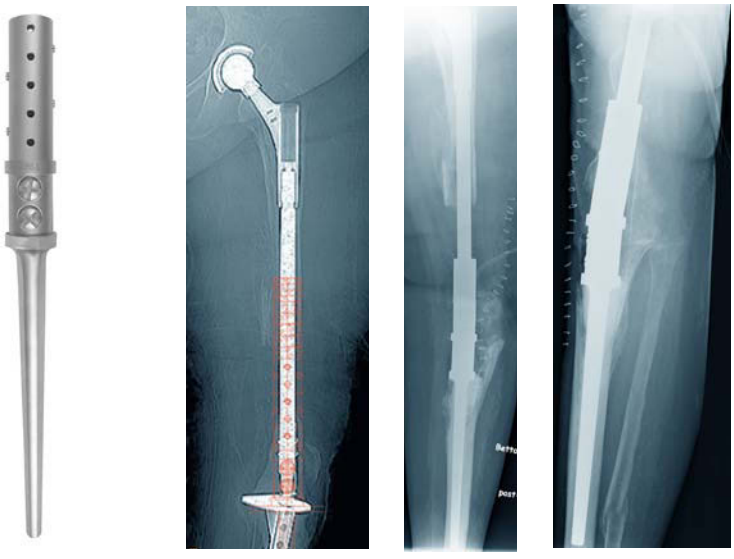
Topical antibiotic treatment with cemented version

The LINK® Endo-Model® Knee Fusion Nail SK is implanted like a hinged knee prosthesis with a modular stem. In the event of infection, targeted topical antibiotic treatment is achieved via the cement. The Knee Fusion Nail comprises a femoral and a tibial component, securely connected by a special coupling. It is available in cemented and cementless versions. The stems of the cemented version are tapered, but have three flat planes for anti-rotational stability in the cement bed. The femoral stems are anatomically angled directly behind the coupling. With the cemented models, centralizers ensure correct intramedullary positioning at each end of the nail. Loss of leg length can also be limited because cemented arthrodesis does not require any bone contact.

Illustration opposite: For cemented implantation, the Knee Fusion Nail is available as a two-component system (left) or as a modular version made of an EndoDur® CoCrMo alloy (middle). The version with the LINK PorEx® hard surface modification is ideal for patients with metal hypersensitivity, and is only supplied as a custom-made implant.



Knee Fusion Nail with »RescueSleeve™« as a custom-made implant from LINK

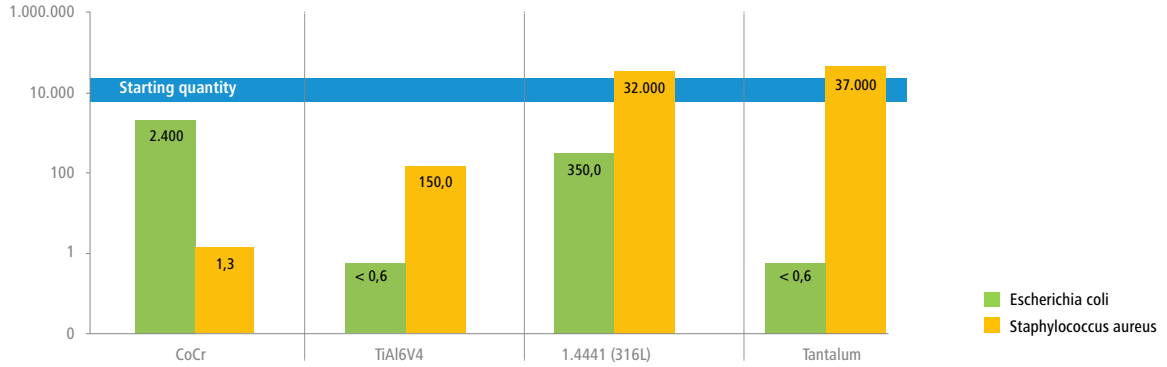


An infected knee prosthesis is replaced by a single-ended Knee Fusion Nail. Sleeve with tibial stem and connection to an in-situ push-through femur following temporary nail splinting with antibiotic application

Osteoconductive and antimicrobial status of the biomaterials used by LINK

Antimicrobial efficacy
as per ISO 22196:2011

- Colony-forming units per cm² after 24 hours incubation
- Only CoCr and TiAl6V4 samples display antimicrobial efficacy against Staphylococcus aureus



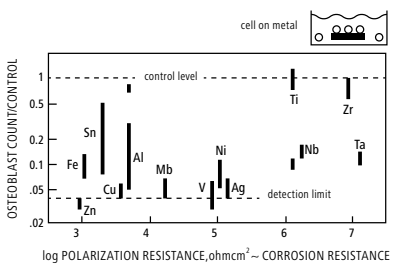
Graph produced from the test results from Eurofins GmbH – see page 23

Biomaterials for joint prostheses should preferably not be cytotoxic and, if intended for cementless anchorage, they should promote the deposition of bone precursor cells. On this basis, Steinemann[1] conducted tests with samples of widely differing materials in cultures with fibroblasts and osteoblasts. The result shows that titanium and zirconium were the only implant materials which supported osteoblast proliferation. Niobium and tantalum, in contrast, greatly hindered growth.[1]

The implant materials employed by LINK today are titanium, principally in the form of Tilastan® (TiAl6V4), cobalt-chromium-molybdenum alloys such as Endo-Dur® (CoCr28Mo6) and, for certain special applications, stainless steel (X2CrMo18-15-3).

These materials have differing antimicrobial properties, in addition to their varying biocompatibility and mechanical properties. There are publications with differing evaluations, and recently tantalum has also been ascribed special antimicrobial properties. In view of this, we arranged for testing of our aforementioned implant materials, and additionally tantalum, with regard to their effect on *Staphylococcus aureus* and *Escherichia coli*. The results showed that all the implant materials tested displayed different effects on Escherichia coli, but only cobalt-chromium and titanium samples displayed a clear antimicrobial efficacy against *Staphylococcus aureus*. Stainless steel and tantalum were ineffective against this pathogen. Below we present a description of the system and procedures of the test conducted by Eurofins in Planegg, near Munich, in Germany.

Helmut D. Link



Results of experiments with osteoblasts cultured on metal discs. The abscissa is the logarithm of the polarization resistance of the metal and depicts its corrosion resistance. The ordinate is the normalized cell count, also in logarithmic scale. Growth inhibition is absent for Ti and Zr, but is strong for corrosion-resistant Nb and Ta. Growth inhibition is observed for all the less corrosion-resistant metals.[1]

[1] Steinemann SG: Compatibility of Titanium in Soft and Hard Tissue – The Ultimate is Osseointegration; Materials for Medical Engineering, WILEY-VCH, Volume 2, Page 199-203.

Testing for antimicrobial activity as per ISO 22196 (2011)

The test materials I, II and III given in the table below were tested for antimicrobial activity in accordance with ISO 22196 (2011) (»Measurement of antibacterial activity on plastics and other non-porous surfaces«). The test is based on a comparison of the growth or elimination of microbes applied to the materials. The materials tested are compared with reference materials with known growth-inhibiting (antimicrobial) properties or with no such properties. TiAl6V4, which is antimicrobially active, was used as an external reference material. Empty petri dishes served as an internal reference material with no antimicrobial activity. *Staphylococcus aureus* (ATCC 6538) was used as the test strain.

The test materials, and also the external reference material, were autoclaved for 15 minutes at 121°C before being used for the test in order to produce a microbe-free test surface. Three samples of each test material were examined. The test surface on the test and reference materials measured 4 x 4 cm. 400 µl of a defined bacterial suspension was applied in drops to all the test surfaces and covered with Parafilm measuring 4 x 4 cm. The bacterial count was performed on three samples of each reference material (external and internal) immediately after applying the suspension (zero-hour value). With three other samples of the reference material (external and internal), the bacterial count was performed after 24 hours.

The ISO 22196 (2011) criteria for the bacterial counts obtained for the reference samples were fulfilled in the test and are detailed below.

- **Criterion 1:** Minimal deviation of the bacterial counts between each group of three samples of the reference materials (zero-hour values).
- **Criterion 2:** Average bacterial count on the reference materials without incubation: between 6,200 and 25,000 CFU (colony-forming units)/cm^2 (zero-hour values).
- **Criterion 3:** Average bacterial count on the reference materials after incubation: still at least around 62 CFU/cm^2 (24-hour value).

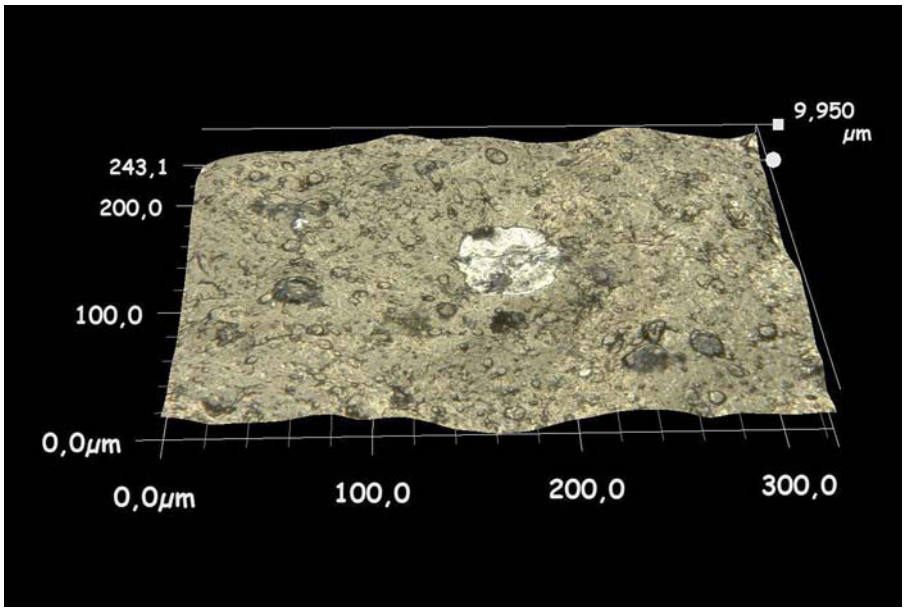
The bacterial count on three samples of each test material was performed after 24 hours. All the bacterial counts were performed doubly. The value R is calculated from the ratio of the bacterial counts obtained. This value is a measure of antimicrobial activity and is defined as $R = U_t - A_t$ (= mean value of the log CFU/cm^2 of the reference material after 24 h − mean value of the log CFU/cm^2 of the test material after 24 h). The material is said to possess antimicrobial activity if R has a value of ≥ 2.

As shown in the table below, the antimicrobial activity of the external reference material (TiAl6V4) in comparison with the internal reference material was confirmed. The same applies to the examined Material I (CoCrMo), whose antimicrobial activity in relation to the internal reference material was almost double that of the external reference material. In contrast, no antimicrobial activity was detected for tantalum or 1.4441 stainless steel.

Mario von Neubeck, Scientist Microbiology
Eurofins BioPharma Product Testing Munich GmbH

Test microbe	Sample	Mean CFU/cm^2 after 24 hours	Log CFU/cm^2 after 24 hours	R (internal reference)	R (external reference)
Staphylococcus aureus **ATCC6538**	Internal reference material	7.0 x 10^4	4.8		
	External reference material TiAl6V4 (blasted with granules)	1.5 x 10^2	2.2	2.6	
	I CoCrMo (glass-blasted)	1.3 x 10^0	0.1	4.7	2.1
	II tantalum (blasted with granules)	3.7 x 10^4	4.6	0.2	-2.4
	III 1.4441 stainless steel (polished)	3.2 x 10^4	4.5	0.3	-2.4

Eurofins BioPharma Product Testing Munich GmbH, Department of Microbiology, Behringstrasse 6/8, 82152 PlaneggMünchen, Germany,
www.eurofins.com/pharma-services, MicrobiologyMunich@eurofins.com



3D image of a PorAg™ pore (center of image) with 1000x magnification

PorAg™ anti-biofilm surface modification from LINK

Revision procedures are statistically associated with a high incidence of periprosthetic infections.[1] Infection prophylaxis is therefore a critical factor for the success of revision and tumor prosthetics. Biofilm formation is the central factor in periprosthetic infections. Apart from systemic antibiotics, silver is used in various ways to prevent biofilm formation on implant surfaces. While silver has virtually no toxicity in the body,[2] free copper is regarded as particularly toxic because it generates highly active, cytotoxic oxygen compounds, thereby causing damage to proteins and lipids.[3] For this reason, LINK exclusively employs silver for its biofilm-preventing surface modification.

Surface modification that is resistant to abrasion and shear forces, particularly for load-bearing implants

LINK® PorAg™ oligodynamic surface modification was developed with the focus on biocompatibility, oligodynamic efficacy, resistance prevention, long-term efficacy in reducing silver particles and silver ions, and good adhesive and shear strength. PorAg™ can be used to modify the surface of soft tissue components for hip, knee and megaprostheses. PorAg™ is applied to implant materials such as titanium, titanium-based and cobalt-based alloys, and AISI 316L implant steel by means of the PVD (Physical Vapor Deposition process. The result is a two-layer surface modification with a thin, very hard cover film, which is suitable particularly for load-bearing implants under a soft-tissue covering. The oligodynamic effect of the implant surfaces is created in a modification approximately 1 µm thick, which comprises an underlayer of silver (Ag)

and an open-pored covering layer of hard titanium-silver nitride (TiAgN) just 100 nm thick.

The surface modified in this way provides a limited supply of silver ions (Ag+) and electrons, whereby the number of protons required on the implant surface for ATP formation is reduced, causing the bacteria to be »starved«. Preclinical tests showed that this produces a significant oligodynamic effect but no toxicity. The active silver ions (Ag+) in the quantity supplied by the surface material are very limited[1,2] and are very largely neutralized by the ambient chloride.

No biofilm, no side-effects in first clinical study

The oligodynamic efficacy of PorAg™ was preclinically tested and confirmed with *Staphylococcus aureus* as the most effective biofilm-forming pathogen. Prof. Rodolfo Capanna contributed initial study results for the clinical use of PorAg™ [4]. In 37 patients who, between 2010 and 2014, received a LINK® Megasystem-C® with PorAg™ components following an infection, no biofilm formation was found on the in-situ implants. Nor were any side-effects observed. The measured circulating silver levels confirmed both the persistence of the silver coating activity after three years and also the safety of silver-coated implants. Further studies are to follow.

[1] Mortazavi et al.: Revision Total Knee Arthroplasty Infection, Clin Orthop Relat Res (2010) 468:2052–2059

Double layer of Ag and TiAg20N = PorAg™. In contrast to other silver-containing surface modifications, the TiAlV/Ag/TiAgN system developed by LINK is resistant to shear forces, thanks to the PVD technology. The antimicrobial effect is based on the silver present in the underlayer and integrated into the hard covering layer

[2] Lansdown, AB.: »Silver in health care: antimicrobial effects and safety in use.«, Curr Probl Dermatol. 2006;33:17-34.

[3] Brewer GJ.: »Copper toxicity in the general population.«, Clin Neurophysiol.,2010 Apr;121(4):502-7

[4] Prof. Rodolfo Capanna, II Clinica Universitaria Ortopedia e Traumatologia, Pisa

In a recent lab evaluation PorAg™ proved to be effective against:

- *Staphylococcus aureus* [5]
- *Escherichia coli* [6]
- *Staphylococcus epidermidis* [7]
- *Pseudomonas aeruginosa* [8]
- *Staphylococcus aureus MRSA* [9]

(Germ reduction 99,9% – Log >4)

Reports of the company QualityLabs BT GmbH:

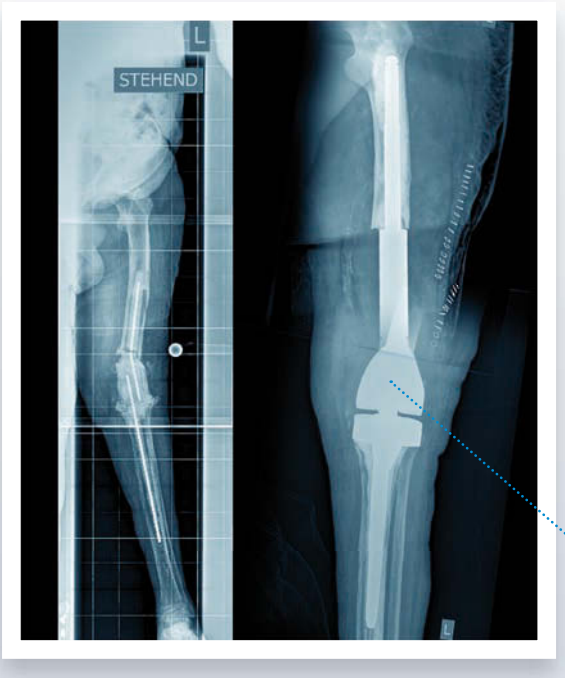
[5] Report no. 160606-10237-22196-01
[6] Report no. 160606-10237-22196-02
[7] Report no. 170206-10237-22196-01
[8] Report no. 170207-10237-22196-01
[9] Report no. 170208-10237-22196-01

LINK® MEGASYSTEM-C® modular tumor and revision system with PorAg™ components

The PorAg™ surface modification from LINK is only available as a customized solution:

PorAg™	TiAgN/Ag = titanium-silver nitride/silver surface modification	Anti-biofilm surface modification for use with bone-replacement implants in the soft tissue

Providing over 35 years
of intrinsic stability after clearing infection



The LINK® Endo-Model® Rotational and Hinge Knee Prosthesis offers several options once the knee joint infection has been eliminated. The dimensioning of the Endo-Model® means that it is a knee prosthesis that requires very little bone resection and permits maximum preservation of bone substance. It can be used for both revision and primary procedures, and also as a basic for a custom-made prosthesis. The images show a LINK® Megasystem-C® push-through prosthesis with a long distal femur replacement. The Endo-Model® has a thicker standard modular stem for the tibia. The design with the head-neck section is designed to facilitate a potential conversion to a total femur replacement.