

EXACTECH | **SPACER**

Design Rationale



InterSpace®

Pre-formed Spacer System



InterSpace®

First Pre-Formed Spacer System

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“The battle against infection is as old as human civilization. The last few centuries have benefited from great scholars such as Louis Pasteur, Ignaz Philipp Semmelweis, Alexander Fleming, and Joseph Lister. As a community, there has been a transformation in the practice of medicine with extraordinary discoveries. However, the challenge to prevent infection following surgery remains unaccomplished.”¹

– Parvizi MD, FRCS, Javad. *MSIS Consensus Proceedings*, 2013.

The Infection Challenge

Surgeons must overcome patient complexities with various co-morbidities, severe bone loss and unidentified organisms. By means of patient history, physical exams, lab and serological testing, and joint aspirations, among other considerations, surgeons have no definitive modality for diagnosis and treatment. In 2013, the Musculoskeletal Infection Society (MSIS) organized a consensus meeting with some 400 delegates from 52 countries comprised of smaller work groups. The mission was to reach consensus on topics surrounding PJI that lack higher level evidence. The delegation summarized the following criteria for diagnosis:¹

1. Two positive periprosthetic cultures with phenotypically identical organisms OR
2. A sinus tract communicating with the joint OR
3. Three of the following minor criteria:
 - Elevated serum CRP and ESR.
 - Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip.
 - Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%).
 - Positive histological analysis of periprosthetic tissue.
 - A single positive culture.

Periprosthetic joint infection (PJI), with all its disastrous consequences, continues to pose a challenge to the orthopaedic community. Practicing orthopaedic surgeons have invested great efforts to implement strategies that may minimize surgical site infection (SSI). Although high-level evidence may support some of these practices, many are based on little to no scientific foundation. Thus, there is a remarkable variation in practices across the globe for prevention and management of PJI.¹ — Parvizi MD, FRCS, Javad. MSIS Consensus Proceedings, 2013.



Out of the 16,665 hip procedures, 3.4% were revisions.
Of the revisions, ± 38% infected.



Out of the 27,158 knee procedures, 3.1% were revisions.
Of the revisions, ± 46% infected.



Prevalence and Economic Burden

In 2013, the American Joint Replacement Registry reported infection as the most devastating complication in total joint arthroplasty. The report demonstrated that the number one reason for hip and knee revisions, with nearly 38 percent of hip and 46 percent of knee, stemmed from infection.² By 2020, hip and knee infections will surpass 60,000 procedures and are expected to cost hospitals in excess of \$1.6 billion annually (see Charts 1 and 2).³

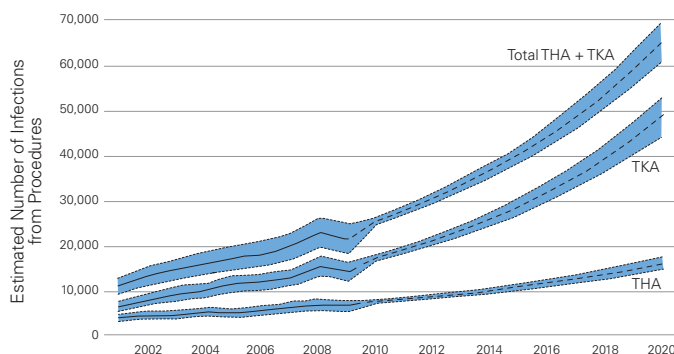


Chart 1. “Historical and projected number of infected THA, TKA, and total (THA + TKA) procedures in the United States (2001-2020). The dashed lines represent the projected values per surgery type, and the dotted lines represent the 95% CIs of the historical estimates (2001-2009) and the statistical projections (2010-2020).”³

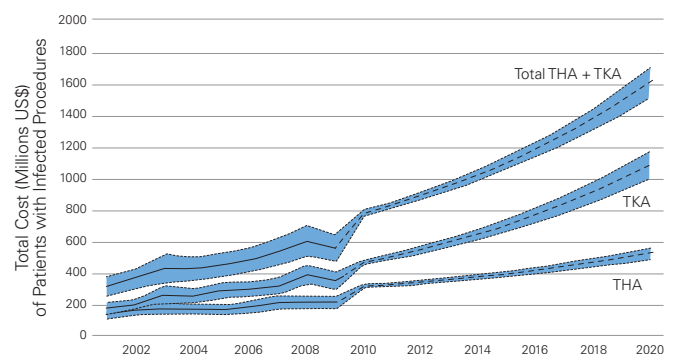


Chart 2. “Historical and projected total inpatient cost of infected THA, TKA and total (THA + TKA) procedures in the United States (2001-2020). The total cost (in millions of USD) is adjusted to 2011 using the Consumer Price Index. The dashed lines represent the projected values per surgery type, and the dotted lines represent the 95% CIs of the historical estimates (2001-2009) and the statistical projections (2010-2020).”³

Evolution of Antibiotic Spacers

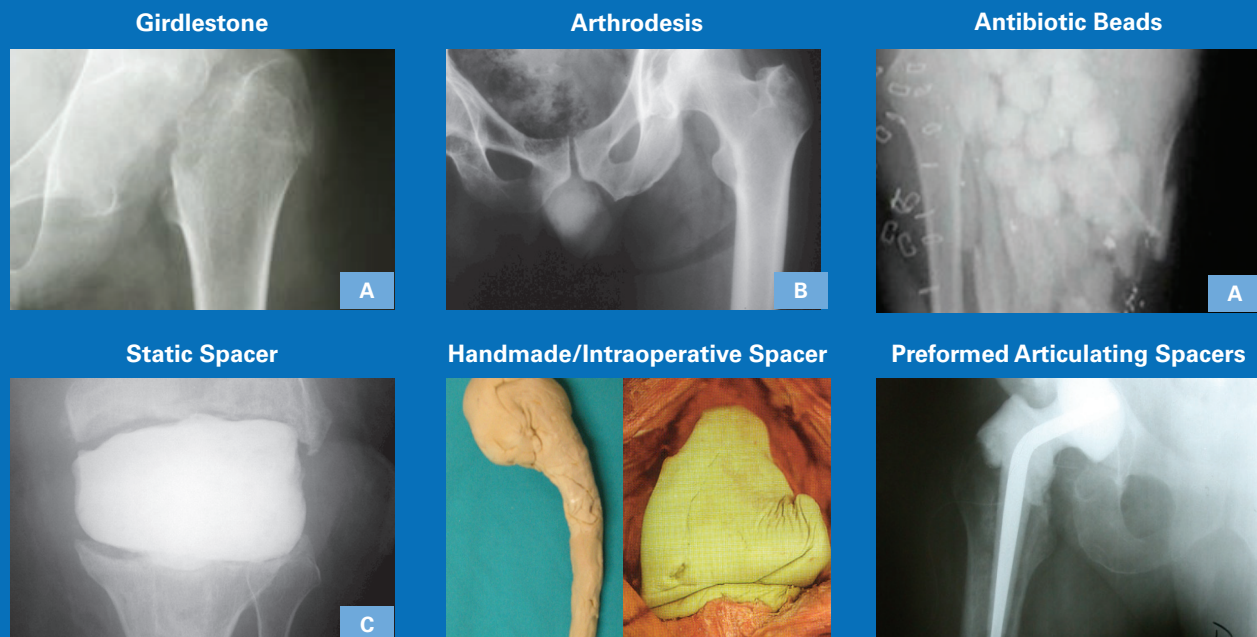


PHOTO SOURCE CREDITS: A. bonesmart.org B. Whitehouse, M. R., & Duncan, C. P. (2013). Conversion of hip fusion to total hip replacement. *Bone Joint J*, 95-B(11 Supple A), 114-119. Accessed February 24, 2017. <https://doi.org/10.1302/0301-620X.95B11.32908>. Reproduced with permission of British Editorial Society of Bone and Joint Surgery via PLS Clear. C.J Bone Joint Surg Am, 2007 Apr; 89 (4): 871 -882 . <https://doi.org/10.2106/JBJS.E.01070>

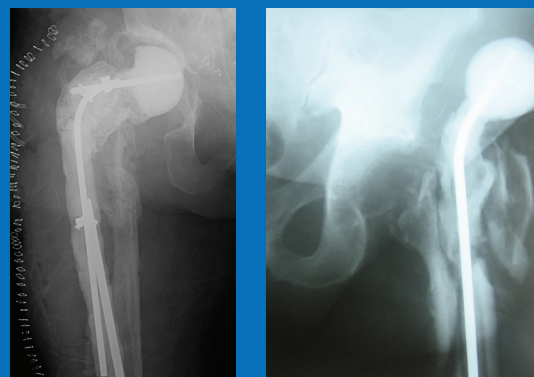
Dating back three decades, it was possible to see surgeons modeling bone cement in the operating room with their hands to obtain devices that mimicked the geometries of permanent prosthesis. The devices were created to temporarily replace a prosthesis removed due to a septic process. The goal for placing the antibiotic bone cement device in the infected site aimed to bolster the systemic antibiotic therapy, because the systemic therapy does not always guarantee optimal antibiotic concentration in the infected joint. The device would later be revised to a definitive prosthesis. The result gave the patient a joint free of infection and a return to some form of functional recovery. Today, this device is known as a "spacer."⁶⁻⁹

VARIOUS TREATMENT MODALITIES

In order for surgeons to tackle the great PJI challenge, they have become inventive and developed various treatment modalities to help patients. Today, the current gold standard is a two-stage exchange arthroplasty, averaging success rates between 82 and 96 percent.⁴ Surgeons can choose to use either a static or articulating spacer. Articulating spacers provide the patient with added benefits, such as maintaining the joint space between the first- and second-stage procedures, increased function and comfort when moving, and preventing joint, muscle and tissue contracture.⁵

Mechanical Failure

Over the years, the techniques for making handmade antibiotic spacers intraoperatively improved as the experience of surgeons grew along with the increased availability of better tools and instruments. Unfortunately in many cases, it was possible to have bad experiences due to the mechanical failure of handmade devices. Although breakage was a feared and undesired complication, surgeons were very satisfied with the antiseptic effectiveness that antibiotic spacers provided. In other words, the spacer and the systemic treatment increased the probability of success compared to systemic antibiotic therapy alone.



Design History

InterSpace® Knee, Hip and Shoulder are preformed, articulating, partial load-bearing structures comprised of gentamicin-impregnated PMMA bone cement. InterSpace is indicated for skeletally-mature patients undergoing the first stage of a two-stage revision arthroplasty.

INTERSPACE® HIP

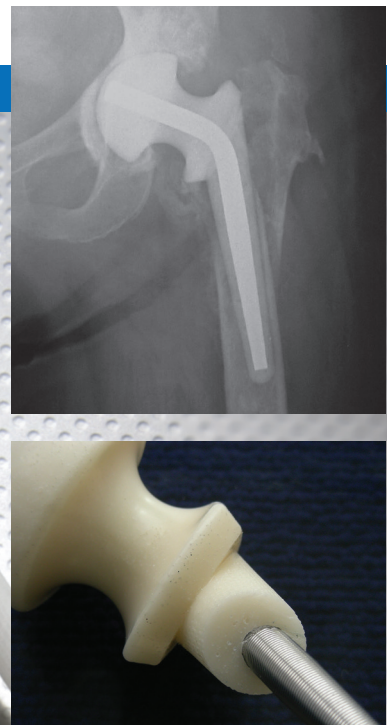
As the flagship product of InterSpace, InterSpace Hip (Spacer-G) was the first spacer introduced to the market. Its positive clinical results coupled with the systematic research of surgeon-made devices led to the design of products that could be both mechanically safe and pharmacologically effective. Simply put, the aim was to create a “reproducible and effective device” that could also provide a better quality of life for patients.

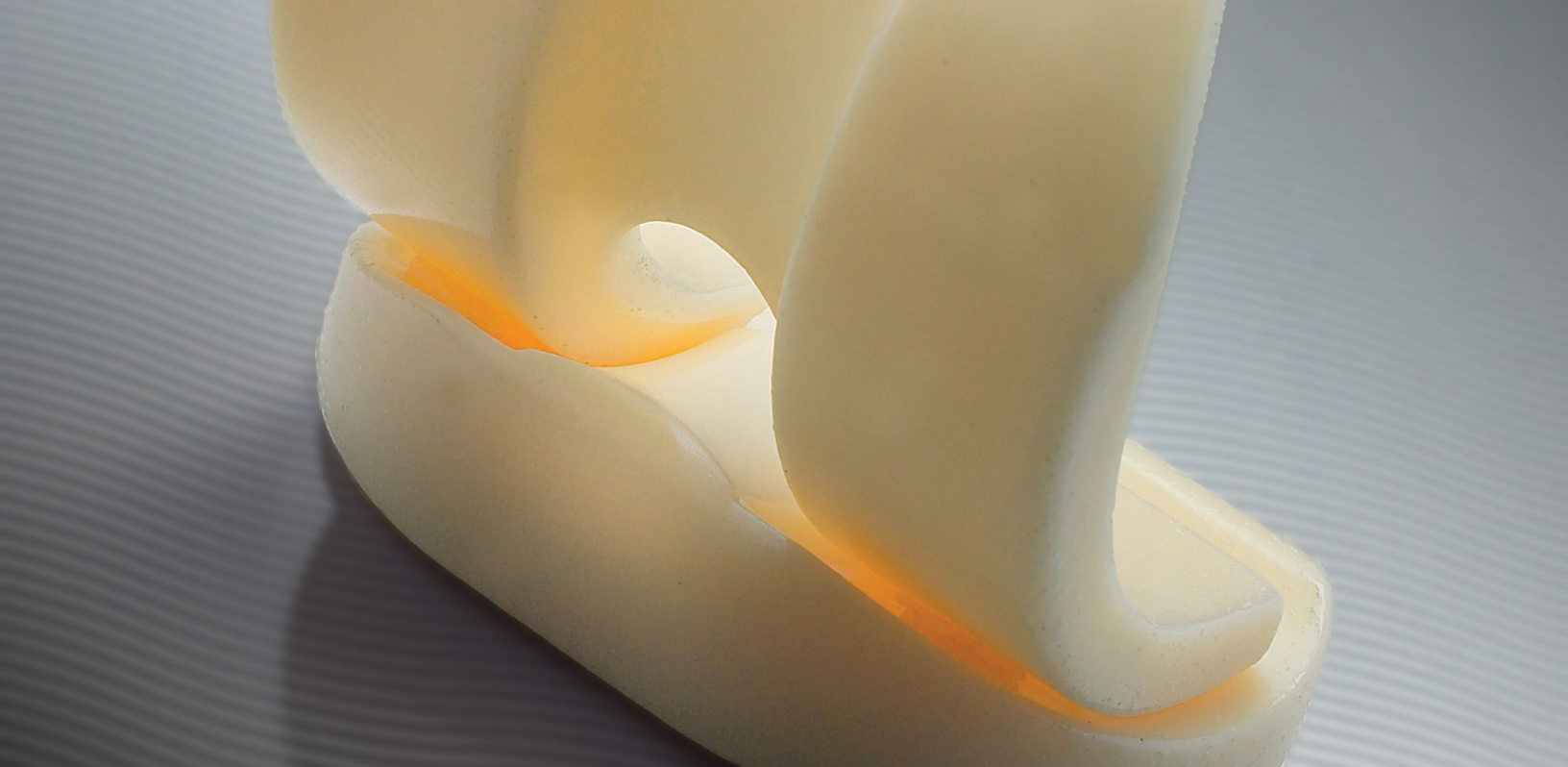
With these key features, the InterSpace Hip was designed. Its geometry was studied to permit an optimal interaction between the acetabulum and the femur. The anatomical stem-neck angle was chosen to limit dislocation as much as possible; the saddle shaped neck was designed to limit the possible acetabular protrusion; and the extreme smoothness of the head was intended to reduce the possible generation of debris. An inner

stainless steel bar (Figure 1) was inserted to provide high mechanical strength, and gentamicin was the chosen antibiotic due to the wide spectrum of activity and the respectable release properties of PMMA.

This device allowed for partial weight bearing and a consistent release of antibiotic in the infected site, which were confirmed with mechanical and pharmacological testing.¹⁰⁻¹⁴ The initial successes during the first cases led to the expansion of product offerings. The addition of head size options improved the head-acetabulum coupling and reduced dislocations. In addition, a long-stemmed version was introduced, allowing surgeons to use the device in the absence of proximal support, in the presence of large metaphyseal defects, and after a transfemoral explantation approach.¹⁵

Figure 1. Inner core present in InterSpace Hip





INTERSPACE® KNEE AND SHOULDER SPACERS

The clinical success of the InterSpace Hip led to the designs of InterSpace Knee and InterSpace Shoulder.

InterSpace Knee (Spacer-K) resembles an ultracongruent condylar knee prosthesis, consisting of two articulating independent elements. Following component removal and debridement, the femoral component articulates on the tibial component, which has a flat base. InterSpace Knee is affixed with Cemex®, gentamicin PMMA bone cement, to the remaining femoral condyles and the proximal tibia.

The InterSpace Shoulder (Spacer-S) is similar in construct to the InterSpace Hip. The shoulder is an unipolar hemiarthroplasty made of gentamicin-impregnated PMMA bone cement and reinforced with a stainless steel core.

These temporary spacers are CE marked as Class III devices and are the first device of its kind to have achieved FDA clearance (InterSpace® Hip; InterSpace® Knee; InterSpace® Shoulder), serving as the precedent for all commercial products that follow.



Design Philosophy

InterSpace was designed to provide patients with a higher quality of life and surgeons with a greater sense of control during their attempted treatments of PJI. These preformed spacers provide infection control by administering a consistent antibiotic release and offer patient mobility through a solution that is efficient and convenient.¹⁶

INFECTION CONTROL

Bone Cement Elution from PMMA

Experimental observations show conditions that lead to an increase or the decrease in antibiotic release. Assuming the solvent and temperature are fixed, the antibiotic release increases when:¹⁶

- The concentration of antibiotic in PMMA increases.
- The surface at the interface cement-solvent (bodily fluids) increases.
- The permeability of the cement matrix increases.

Therefore, if we want to increase the antibiotic release, it is sufficient to increase the diffusion at the interface area. This was the logic followed when designing the second generation High Release spacer.¹⁶



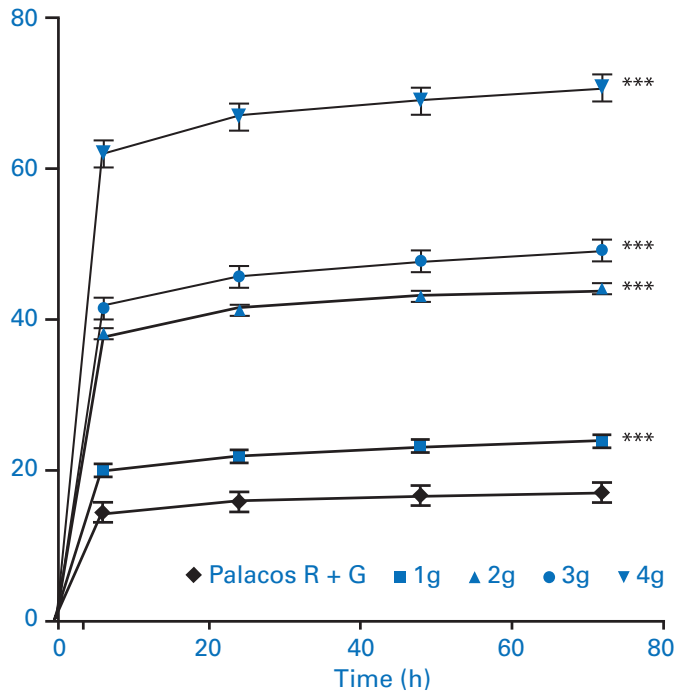
Figure 5. Factors influencing the release of antibiotic from a PMMA matrix.



Figure 6. $\text{Permeability} = \text{Porosity} + \text{Chemical/Physical Properties (of matrix)}$



Chart 3. Cumulative Gentamicin Release¹⁷



Gentamicin Release Rates from Manufactured Bone Cement

A study was conducted on gentamicin release as a function of time for unloaded Palacos R and Palacos R loaded with additional gentamicin. Among the bone cements tested, gentamicin release was most rapid during the first six hours and continued at a much lower rate thereafter. The incorporation of additional antibiotics does result in an initial increase in antibacterial activity compared to standard antibiotic-loaded bone cement; however, this beneficial effect is no longer apparent by 72 hours as clinical isolates form biofilms on the bone cements despite the initial release of high levels of antibiotic. The incorporation of additional gentamicin into traditionally-mixed PMMA bone cement does not appear to be an effective method for the treatment of overt infection at the time of revision surgery (Chart 3).¹⁷

High Release Matrix

In 2006, the first spacers with increased antibiotic release were distributed. The absolute amount of antibiotic found in the first generation device is identical to today's version; however, the new product offers an increased release capacity known as the High Release formulation. The elution can be as high as four to five times the release of the previous generation. This result has been achieved in two ways:¹⁶

1. The external surface (i.e., the interface area with the biological liquids) has been increased thanks to a special finishing that increases the surface area (Figure 4).¹⁶
2. The bone cement matrix that includes the antibiotic is made with a new generation of polymers structured to increase permeability (Figure 5).¹⁶

The spacer's textured surface has an increased surface area, which allows for greater antibiotic release. Also, its enhanced permeability increases the release through a new generation of polymers.

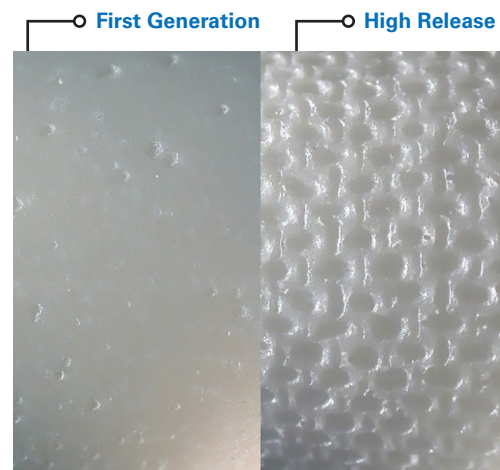


Figure 4.

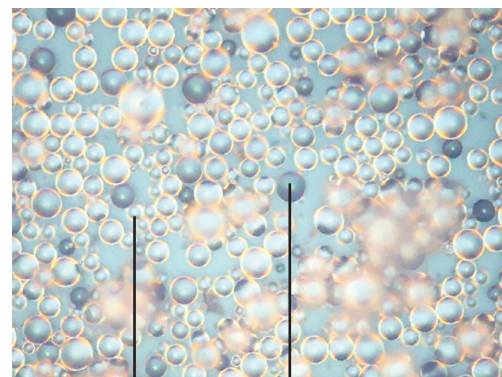


Figure 5.

PMMA
Pearls

Gentamicin
Sulphate Pearls

Consistent Local Antibiotic Release: Protection Against Bacterial Colonization

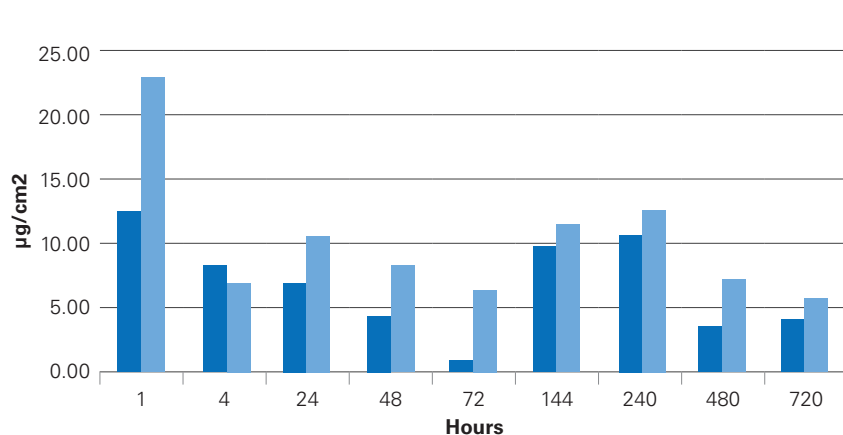
During the first few days following implantation of InterSpace, the local pathogenic microbial load is reduced, both with the removal of the infected prosthesis and of all necrotic and infected tissue. The local gentamicin release provided by InterSpace in these very first days following intervention is fundamental for treatment as it provides antibiotic coverage for surrounding tissues and joint fluid that have been compromised.

InterSpace is engineered to provide:

- A continuous presence of antibiotic on the device which prevents bacterial colonization for the six-month FDA-cleared life of the device.

- A local antibiotic release during the interval following the spacer implantation that helps to avoid systemic toxicity.¹⁸
- Antibiotic levels in the fluid surrounding the joint that maintain minimum inhibitory concentration (MIC) levels throughout the duration of implantation, reducing the risk of developing resistant bacteria.^{17,19}

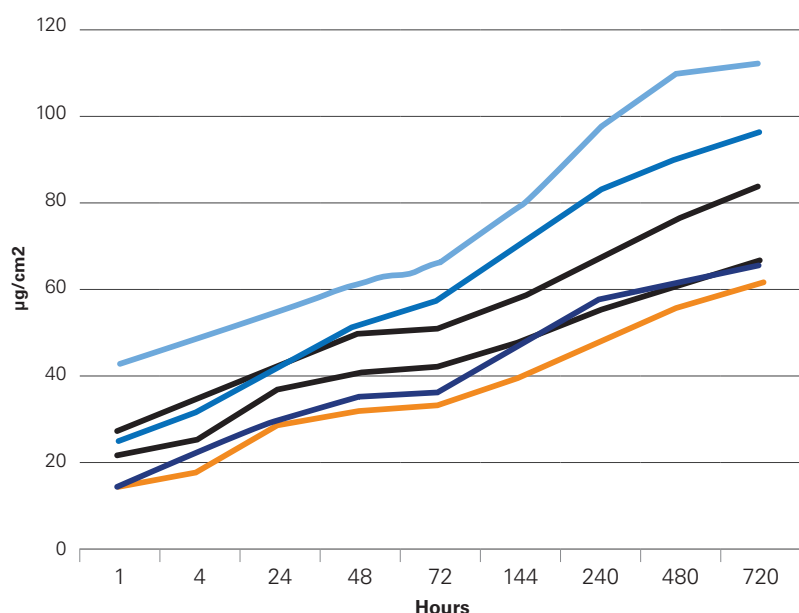
A sustained, high local concentration is delivered to reduce the risk of developing resistant organisms. The InterSpace design allows for a consistent and sustained release of gentamicin in the infected joint, maintaining MIC and therapeutic levels beyond the first days of implantation (Charts 4 and 5).^{17,19,20}



■ InterSpace Hip 46XL
■ InterSpace Hip 54XL

Chart 4. In-Vitro Incremental Gentamicin Release

In this chart, InterSpace is shown to release 1,500µg/day for the first 10 days and exceeds 500µg/day for the following 20 days. The values can be directly compared to MIC values where the gentamicin susceptible threshold is less than or equal to 4µg/ml.²¹



■ InterSpace Hip 46
■ InterSpace Hip 54
■ InterSpace Hip 60
■ InterSpace Hip 46XL
■ InterSpace Hip 54 XL
■ InterSpace Hip 60 XL

Chart 5. In-Vitro Cumulative Gentamicin Release

This chart illustrates the cumulative antibiotic release that takes place during the first 30 days. It should be stated that the actual in-vivo release is likely to be higher due to friction, despite acceptable wear properties.¹⁰ Additional biological release can be influenced by the joint activity (i.e. weight bearing, limb mobility), dynamic fluid flow system and tissue absorption capability.^{12,19}

BIOLOGICAL EFFECTIVENESS

Antimicrobial Activity of Gentamicin

Gentamicin's antimicrobial activity covers both Gram-positive and Gram-negative bacteria (Chart 6).²² This wide spectrum of biological coverage makes gentamicin the antibiotic of choice when treating endoprosthetic infections with PMMA. Further criteria that substantiate gentamicin as a suitable antibiotic in bone cement are as follows:²²

- Active substance with bactericidal properties.
- Thermal stability during polymerization.
- Chemical stability during the exposure to monomer.
- Molecular size ideal for release from the bone cement matrix.
- Low influence on mechanical properties of cement.
- Low potential for allergic reaction.

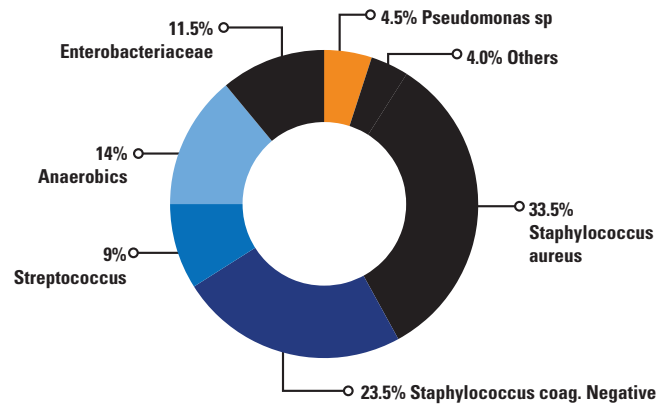
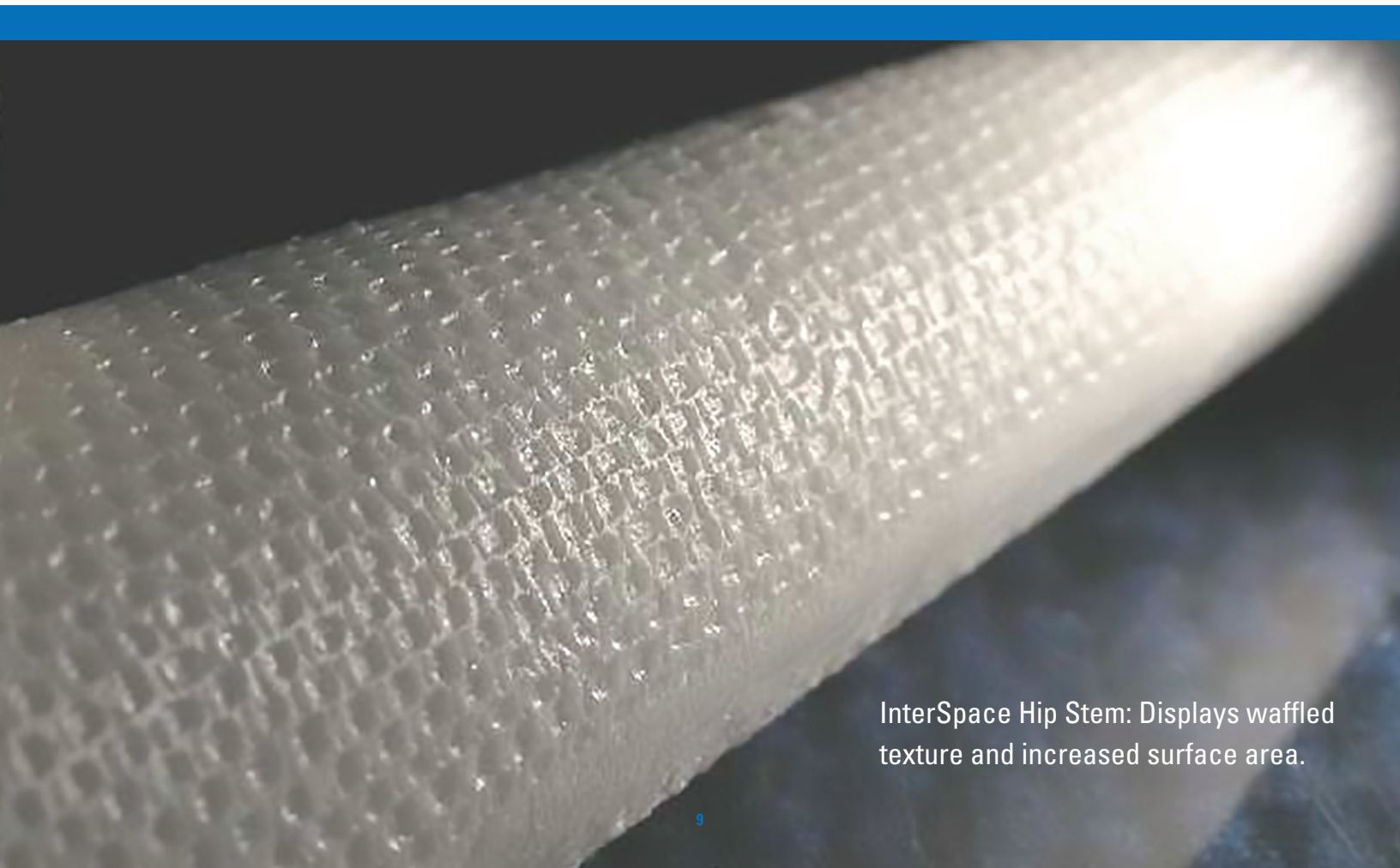


Chart 6. Gentamicin Spectrum of Coverage:

InterSpace also covers a wide spectrum of biological coverage, including both Gram-positive and Gram-negative bacteria.²²



In-Vivo Gentamicin Levels from InterSpace

A study measured gentamicin levels after an extended period following in-vivo implantation.¹⁹ All patients had a positive microbiology diagnosis with 10 being coagulase negative staphylococcus, and the remaining two being staphylococcus aureus. An antibiotic-loaded, articulating spacer (Spacer K, Tecres IT; InterSpace Knee, Exactech) was implanted using antibiotic-loaded cement containing gentamicin. Patients followed a 14-day regime of parenteral antibiotics followed by four weeks of oral antibiotics. None of the patients received additional gentamicin.

During the second-stage revision, venous blood samples were taken for gentamicin assay. Following this, the InterSpace was removed at a median interval between the first and second stages of 99 days (range 63-274

days). Gentamicin was detected in all synovial fluid samples with concentrations ranging from 0.24-2.36 mg/L (1 mg/L is equivalent to 1 µg/ml). This data shows that InterSpace is effective at delivering therapeutic levels of antibiotics in-vivo between the first and second stage of total knee arthroplasty (Chart 8).¹⁹

Its reliability and consistency are derived in part from its High Release formulation. The preformed spacer releases therapeutic levels of gentamicin, exceeding minimum inhibitory levels, throughout the period of implantation. The High Release formulation was designed to provide an effective local release of antibiotics that reduces the risk of antibiotic-resistant bacteria while avoiding systemic toxicity.^{16,19}

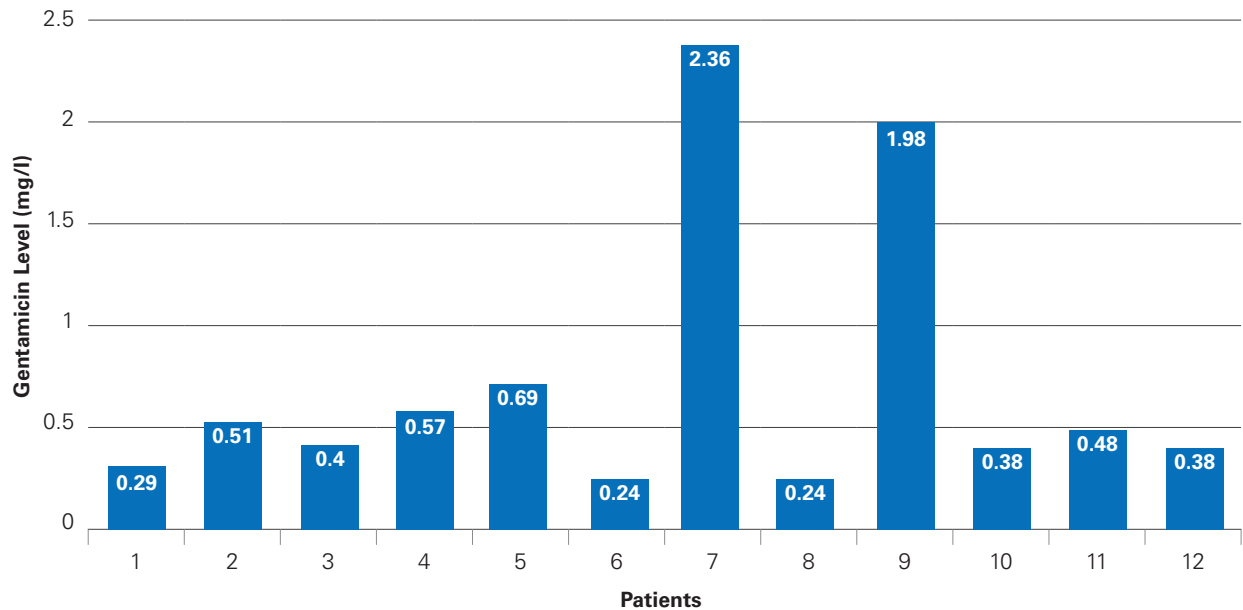


Chart 7. Gentamicin Levels at Second-Stage Revision
Measurements of in-vivo intra-articular gentamicin levels from a pre-formed, antibiotic-loaded, articulating spacers (Spacer K, Tecres IT; InterSpace Knee, Exactech) in revision total knee replacement.¹⁹



PATIENT MOBILITY

The stainless steel core, found in both the hip and shoulder spacers, provides a more robust mechanical structure. Patients gain mobility through the articulating spacer and can perform limited weight-bearing activities.

Patient Mobility Provided by Mechanical Integrity

InterSpace is designed to provide an articulating, functional spacer similar to a hemi-hip prosthesis, an ultra congruent condylar knee or total shoulder arthroplasty. InterSpace facilitates the maintenance of the joint space and allows some joint function, including partial weight bearing. The mechanical safety and effectiveness that deliver patient mobility are as follows:

- Maintains joint space and allows limited mobility with partial weight bearing.^{23*}
- Geometry allows for temporary joint function comparable to a definitive prosthesis.
- Mechanical resistance comparable to a definitive prosthesis given the six-month FDA-cleared indication of the device.²⁴

- Fatigue and wear resistance allows for partial load-bearing between stages.^{16,24}
- Stabilizes or tensions the soft tissues and reduces bone loss between stages, potentially facilitating easier re-implantation during a second-stage procedure.^{21,25-27}
- Reduces hospitalization and allows for an early transition to rehabilitation and physical therapy.^{14,26}
- Improves quality of life between procedures.^{16,25,27,28}
- Offers functional success rates equivalent to non infected revisions.²⁹

InterSpace Hip, Knee and Shoulder prevent muscle, joint and tissue contracture, while keeping the patient's limb length intact (see Chart 8).^{26,29}

	Aspectic Group	Septic Group
Harris Hip Score (Δ post-op minus pre-op)	54.9	56.2
Leg Length Discrepancy (post-op)	1.3 + -0.6	1.5 + -0.7

Chart 8. Two-stage revisions for infected hip prostheses using a pre-formed, antibiotic-loaded cement spacer and uncemented revision prosthesis offers medium-term success rates equivalent to one-stage non-infected revision.²⁹

Summary of Clinical Experience

InterSpace shows its reliability, efficiency and effectiveness when treating joint sepsis with the global compilation of clinical evidence from more than 25 peer-reviewed papers and nearly 20 different sites. In 2013, a review was conducted by Romano et al, evaluating InterSpace's published results in the public domain:³⁰

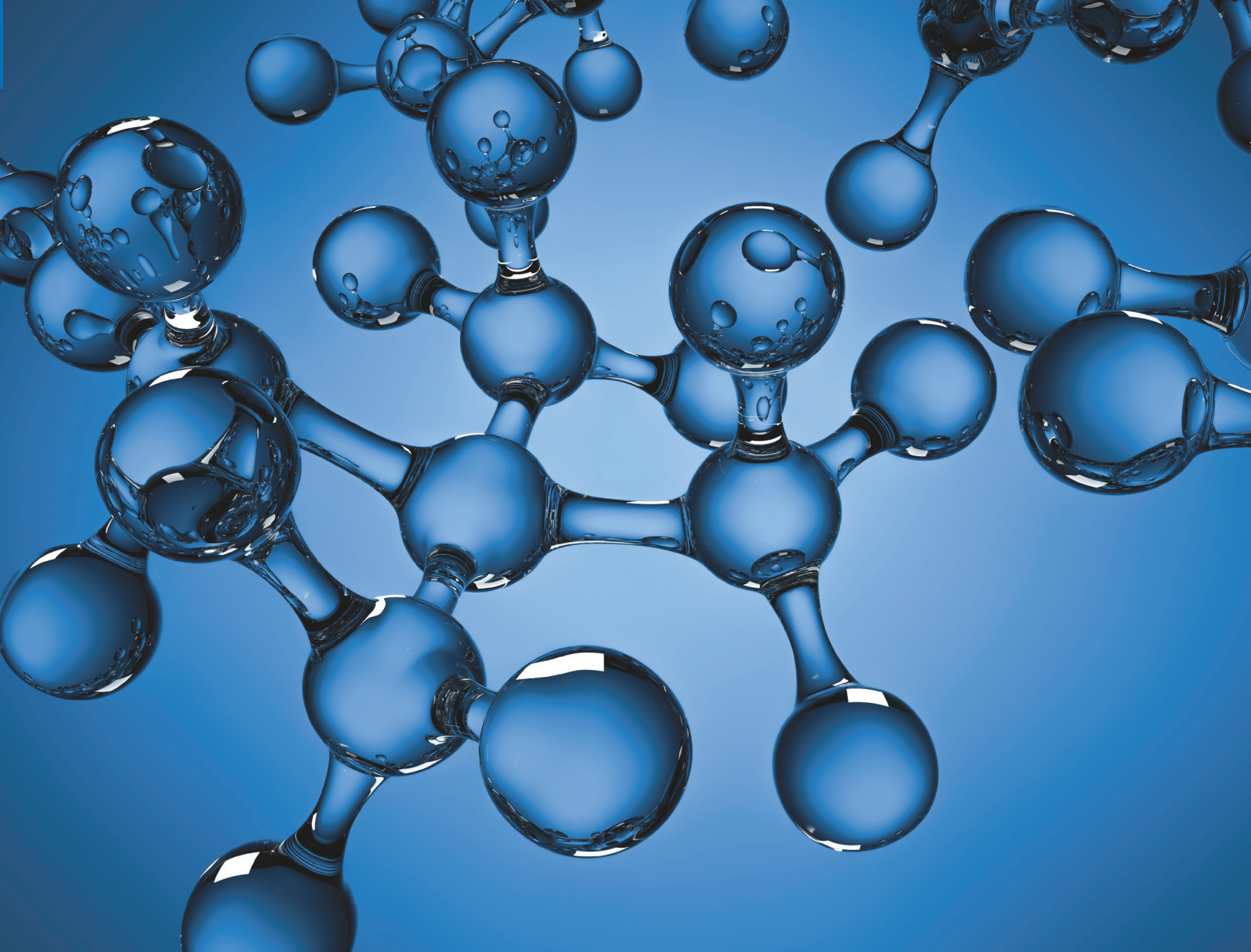
This systematic review provides evidence in favor of the routine use of an industrially, preformed spacer loaded with a standardized, relatively low concentration of gentamicin, [and] that in different centers, showed an average infection eradication rate of 96.1 percent at spacer removal and 94.8 percent at the latest follow-up after reimplantation. The systematic review does not support the hypothesis that the antibiotic associations or antibiotic concentrations higher than 1.9 percent are routinely needed for spacers used in two-stage revision surgery.³⁰ — Romano, CL, Proceedings from Musculoskeletal Infection Society, 2013.

The inclusion criteria removed case reports, clinical series with less than 10 patients, duplicate studies, and series with a mean follow-up of less than 24 months. The exclusion criteria left 10 papers for a total of 491 spacers implanted at 10 centers.³⁰ As the most widely studied spacer technology in the world, this systematic review of the literature demonstrates the safe and effective use of InterSpace in overcoming complications associated with PJI. Despite InterSpace being characterized as a low dose solution, the large clinical data set has shown 94.8 percent infection control at an average of 46 months follow up.³⁰

- Only 19 patients (3.9 percent) had a persistent infection that required a spacer exchange or resection arthroplasty.
- Four hundred and eighty (480) patients underwent the second-stage procedure.
- Of the 480, only 25 patients (5.2 percent) had an infection at the mean follow-up of 46 months.

Journal	1st Author	Type	N.pt	Recurrence/Persistence of infection at spacer removal	N. pts reimplanted	N. pts with no recurrence	FU (mean)	FU (min - max)	Center
Int Orthop (2005)	Pitto RP	Knee	21	1	19	19	24	12 - 43	Auckland (NZ) Bergamo (ITA)
Hip Int (2010)	Gil Gonzalez S	Hip	35	0	35	30	32	6 - 65	Barcelona-1 (SPA)
Int Orthop (2011)	Pattyn C	Hip	61	6	61	59	36	9 - 84	Ghent (BEL)
BMC Infect Dis (2011)	Romanò CL	Hip	20	0	20	19	57	24 - 104	Milan (ITA)-1,2
Musculoskelet Surg (2011)	D'Angelo F	Hip	28	1	27	27	53	18 - 106	Varese (ITA)
J Arthroplasty (2012)	Neumann DR	Hip	42	2	42	41	67	36 - 120	Salzburg (AUT)
J Arthroplasty (2012)	Wan Z	Knee	33	2	31	28	44	24 - 62	Houston, TX (USA)
CORR (2012)	Degen RM	Hip	33	3	30	28	43	24 - 70	London, ON (CAN)
Hip Int (2012)	Romanò CL	Hip	183	3	183	173	60	24 - 132	Milan (ITA)-1,2
J Arthroplasty (2012)	Garcia-Oltra E	Hip	35	1	32	31	48	14 - 85	Barcelona-2 (SPA)
TOTAL			491	19	480	455			11 centers
Average							46.4		

Chart 9. Romano, et al. Low-dose gentamicin-loaded spacers are effective for two-stage revision. Musculoskeletal Infection Society (MSIS). 2013 July 30.³⁰



Conclusion

The placement of an antibiotic spacer as part of a two-stage process has become the gold standard and most effective option for treating joint sepsis.^{25,26} The constant work carried out over the years has led to an extension of the use of bone cement in fields hardly imaginable a few years ago. Today, it is possible to manufacture these medical devices with different properties so that it can be modulated at will. Bone cement can now be designed as a drug delivery system and achieve specific elution kinetics.¹⁶

InterSpace can help standardize the treatment protocol given the preformed nature of the product; and now, InterSpace High Release answers the question of an extended microbiological release beyond that which can be achieved from intra-operatively mixed cement.^{17,19,20} InterSpace delivers therapeutic levels of antibiotic due

to the increased porosity of the device without limiting or weakening the mechanical structure. The technology and precision behind both the mechanical and biological benefits of InterSpace remain novel in the industry and offer continued clinical success as the most widely studied spacer technology in the world.^{14,16,19,26-31}

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*Partial weight bearing must be assessed on an individual basis with relation to the anatomic condition of the local bone, bone quality and clinical conditions of the patient during rehabilitation stages. Care must be taken to minimize the risk of damaging bone tissue and the implant through excessive weight bearing or forced mobilization.

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