**LITERATURE REVIEW**

**RELEASE OF ANTIBIOTICS FROM POLYMETHYL METHACRYLATE CEMENT**

**Abstract** – The increase in resistance rates to antibiotics of bacteria isolated from infected hip joints, particularly staphylococci, prompted us to investigate the usefulness of antibiotic combinations such as gentamicin plus vancomycin. Cylinder test specimens of polymethyl methacrylate (PMMA) cement (Cemex, Tecres) containing gentamicin alone, vancomycin alone and both drugs in combination, were studied. The antibiotic concentrations were determined using a microbiological method and fluorescence polarization immunoassay (FPIA). The release of gentamicin alone, vancomycin alone and in combination from PMMA cement was prompt. The combination revealed synergistic antimicrobial activity against *Escherichia coli* and *Enterococcus faecalis*. FPIA showed that gentamicin and vancomycin delivery rates from PMMA cement were different. Gentamicin alone and in combination with vancomycin presented similar release rates from PMMA cement (1.50%). Vancomycin release from PMMA cylinders impregnated with the combination was lower (0.51%) than that from cylinders with vancomycin alone (1.16%). Vancomycin showed a 34.1% loss of microbiological activity at 37 degrees C after 10 days of incubation; the reduction corresponded to 15.0% when measured by FPIA. Results obtained with test specimens are indicative for the preparation of antibiotic-impregnated cements for different human prostheses.

**Key Quote** – “Novel and recent local drug delivery systems are proposed to improve the local drug release i.e. biodegradable carriers for different drugs with promising results requiring further specific evaluation.” (p. 499)

**TREATMENT OUTCOME OF TWO-STAGE REVISION TOTAL HIP ARTHROPLASTY FOR INFECTED HIP ARTHROPLASTY USING ANTIBIOTIC-IMPREGNATED CEMENT SPACER**

**Abstract** – Infected hip prosthesis, a serious complication of primary total hip arthroplasty (THA), can have severe consequences. We report the treatment outcome of two-stage revision THA for infected hip arthroplasty, including hemiarthroplasty, using an antibiotic-impregnated cement spacer for the interval between the first and second stages. Between 1996 and 2000 we performed this procedure on nine hips in eight patients. Cementless revision THA was performed as the second-stage procedure. Bone defects were restored with frozen allografts. The outcome was evaluated using the hip score of the Japanese Orthopaedic Association (JOA hip score). The mean duration of follow-up was 35.7 months (range 10-55 months). The mean JOA hip score at follow-up improved from 30.1 (range 10-74) to 73.2 (24-96). The mean interval between the first and second stages was 10.1 weeks (range 6-19 weeks). Eight of the nine hips achieved a successful outcome. One hip, with methicillin-resistant *Staphylococcus aureus* infection, experienced recurrence 4 months after revision THA. This patient was successfully treated 14 months after the first revision THA with a two-stage procedure using a vancomycin- and arbekacin-impregnated cement spacer and beads. These results suggest that two-stage revision THA using an antibiotic-impregnated cement spacer is a useful technique for treating infected hip arthroplasty.

**Key Quote** – “Cemex cement subjected to a polymerization temperature of less than 60°C, in PBS (phosphate-buffered saline) after 24h was approximately 182 ug/ml, whereas the amount of VCM (vancomycin) eluted from Surgical Simplex P cement subjected to a polymerization temperature higher than 60°C in PBS after 24h, was approximately 77 ug/ml. That is, the cement subjected to a low polymerization temperature yielded a 2.4-fold higher concentration of VCM than the cement subjected to a high polymerization temperature.” (p. 30)

**FATIGUE STRENGTH OF PMMA BONE CEMENT MIXED WITH GENTAMICIN AND BARIUM SULPHATE VS PURE PMMA**

**Abstract** – Barium sulphate is added to polymethylmethacrylate (PMMA) bone cement as a radiopacifier. Gentamicin is an antibiotic added to bone cement to treat or prevent infection in arthroplasty. This study investigated the combined effect of barium sulphate and gentamicin sulphate on the fatigue strength of PMMA bone cement. Three different formulations were studied: pure PMMA, PMMA with barium sulphate added and PMMA with barium sulphate and gentamicin sulphate added. Before testing all specimens were stored in water at 37 degrees C for at least 15 days to season the PMMA and to elute the antibiotic. Fatigue tests were performed following...
a previously validated procedure. The slope part of the Wohler diagram was obtained and a rough endurance limit was estimated for all three formulations. The experimental data showed that the addition of barium sulphate to PMMA bone cement affected the fatigue strength of the material, whereas addition of gentamicin sulphate to the radiopaque PMMA had no effect on the fatigue properties of the bone cement. While PMMA with barium sulphate added was confirmed to have a reduced fatigue strength when compared with plain PMMA, no detrimental effect was found for the addition of gentamicin sulphate to radiopaque PMMA.

Key Quote – “Different types of antibiotic may have different effects on the fatigue behavior of bone cement.” (Section 4 Discussion)

Exactech Literature # 003C

THE EFFECT OF MIXING TECHNIQUES (MANUAL, CLOSED SYSTEM, VACUUM) ON BONE CEMENT


Introduction – Aim of the study was to compare two bone cements: Cemex XL and Simplex P.

The discriminating factors to evaluate an aspect of the quality of the bone cement were volume, density and porosity changes in time. Cemex XL is also available in a closed mixing system with the brand name of Cemex System. The Cemex System allows the preparation and delivery of bone cement.

In the human body, the bone cement is exposed to liquid. As the authors believe that the liquid is of great influence to the material properties of the bone cement, the tests are performed for both specimens kept in a dry environment and specimens kept in physiologic water.

Three questions are addressed in this report:

• How large is the porosity of Cemex XL relative to Simplex P
• Is Cemex System proper to mix Cemex XL (In other words can differences in density and dimension change of bone cements be related to the preparation method)?
• What is the difference in dimension and desity change of cement kept in a dry environment and kept in water over time?

Key Quote – “Porosity of Cemex ranged from −0.2% (vacuum mixed) and 0.02% (hand mixed); of Simplex P ranged between 2.1% (vacuum mixed) and 2.5% (hand mixed). These differences are significant.” (p. 12)

Exactech Literature # 004C

A COMPARISON OF CEMEX AND PALACOS CEMENT REGARDING MIGRATION, WEAR AND RADIOGRAPHY. A RANDOMISED 5 YEARS RSA STUDY

Nivbrant B, Kärrholm J. Department of Orthopaedics, University Hospital of Umeå and Salgrenska, Göteborg, Sweden.

Introduction – The performance and strength of the bone-cement-implant interfaces depends on a variety of factors, cement penetration depth, surface area and roughness, bone necrosis and membrane formation due to curing heat and toxic substances and also cement properties such as viscosity at cementation, mechanical strength and stress tolerance. This makes it a complex issue to find the best cement for clinical use by laboratory experiments only. Inferior strength at an interface can be detected by RSA as an increased migration of the actual implant and repeatedly has such a migration by several authors shown its clinical relevant in predicting a coming failure. The aim of present study was to compare a low temperature curing bone cement (Cemex) with a standard (Palacos) regarding post operative implant migration and other adverse effect no bone.

Previous lab test have shown 6 degrees less curing temperature, more release of monomer after curing, lower tensile but higher shear strength for Cemex compared to Palacos. However when used in vivo a lot of factors are pre-chilling, installation time, cooling and vacuum-mixing affects the curing temperature.

Key Quote – “Both cements functioned very well. A small tendency to a better fixation of implants was found for Cemex cement, but no differences according to hip scores, BMD (bone mineral density), Zones or lab tests of bone turn-over.” (Conclusion)

Exactech Literature # 005C

TWO-STAGE REVISION TOTAL HIP ARTHROPLASTY USING A VANCOMYCIN-IMPREGNATED CEMENT SPACER IN AN INFECTED HIP JOINT CAUSED BY MRSA


Introduction – The emergence of methicillin-resistant Staphylococcus aureus (MRSA) has made treatment of the infected hip arthroplasty more challenging. We have had success treating these patients with a vancomycin (VCM)-impregnated cement spacer. Mizunuma demonstrated the heat-sensitivity of VCM, bringing into question the impact of elevated temperature upon VCM loaded into bone cement. The objective of this study is to characterize the elution behavior of VCM formulated in low or high temperature bone cement.

Key Quote – “We conclude that the use of a low-temperature cement may be optimal in the treatment of MRSA.” (Discussion)

Exactech Literature # 006C

TECHNIQUE AND TIMING OF TWO-STAGE EXCHANGE FOR INFECTION IN TKA


Abstract – Infection in total knee arthroplasty is a devastating complication. The two-stage exchange procedure has evolved as an effective treatment option. The classification and alternatives to a two-stage procedure are presented. Current diagnosis and monitoring of infection in total knee arthroplasty with laboratory, aspiration, and imaging techniques are reviewed. The timing, technique, and results of a two-stage procedure are discussed. A knee aspiration with synovial fluid cell count and culture may be a useful adjunct. The use of antibiotic-impregnated cement spacers may be considered at the first-stage surgery. Spacers may be static or articulating, intramedullary dowels, preformed or constructed in the operating room, and provide single- or multiple-agent antibiotic (and antifungal) joint space delivery. Proper technique, antibiotic dosing, and indications with these devices will avoid complications between stages. The most common complications encountered with the use of spacers include dislocation/instability, implant extrusion, overstuffing of the patellofemoral and tibiofemoral joints, and implant or periprosthetic fracture. At the second stage of the procedure, surgical exposure, intraoperative frozen sections, assessment of bone and soft tissue defects, the integrity of the extensor mechanism, and implant selection are important factors to consider in the second-stage reimplantation revision total knee arthroplasty. LEVEL OF EVIDENCE: Level V, therapeutic study. See the Guidelines for Authors for a complete description of levels of evidence.

Key Quote – “The authors emphasized that when mobile spacers were used, there was a considerable reduction in the need for more extensive extensor mechanism exposures and tibial tubercle osteotomy.” (p. 170)
Note: This is a very well written article discussing all of the different options physicians have for treating an infection.

**Exactech Literature # 007C**

**GOOD LONG TERM STABILITY WITH LOW MONOMER BONE CEMENT IN TOTAL HIP ARTHROPLASTY. A RANDOMIZED RSA STUDY**


**Introduction** – Low temperature curing cement with less toxic monomers might obtain a better long term fixation to bone. The cement showed lower curing temperature in laboratory and less shrinkage during polymerization (Nivbrant et al. 2001). We reported earlier on the 5 year results which showed excellent stability in both groups. A tendency to less wear for the low monomer cement could be seen. We have followed up the patients and now can report clinical and fixation results after 10 years.

**Key Quote** – “The results confirm our good mid-term results with Cemex cement.”

(Discussion/Conclusion)

**Exactech Literature # 008C**

**InterSpace®**

**DRAINAGE AND SERUM LEVELS OF ANTIBIOTICS FOLLOWING TEMPORARY SPACER IMPLANTS IN TWO-STAGE REVISION SURGERY**


**Introduction** – Polymethylmethacrylate (PMMA) cements impregnated with aminoglycosides and/or vancomycin are currently utilized as local antibiotic carriers in orthopaedic prosthetic infections.

**Aim** – The local and systemic release of gentamicin from temporary spacers loaded with 2.5% gentamicin (Spacer-G) was studied in patients undergoing two-stage revision surgery.

**Key Quote** – “We found that the maximal drug release from spacers occurs within the first few days and that explanted spacers are able to release bioactive antibiotics 3-6 months after implantation.” (Results)

**Exactech Literature # 001I**

**RELEASE OF GENTAMICIN AND VANCOMYCIN FROM TEMPORARY HUMAN HIP SPACERS IN TWO-STAGE REVISION OF INFECTED ARTHROPLASTY**


**Abstract** – AIM: Evaluation of the delivery of gentamicin and vancomycin from polymethylmethacrylate (PMMA) spacers before and after implantation for the treatment of total hip replacement infections. METHODS: Twenty industrially produced spacers containing gentamicin (1.9%) were utilized. Vancomycin (2.5%) immersed in phosphate buffer at 37 degrees C for 10 days. Antibiotic concentrations were determined by fluorescence polarization immunoassay. RESULTS: Gentamicin and vancomycin were still present in all the spacers removed from the patients. The release of gentamicin alone and in combination with vancomycin was in the range 0.05%-0.4% of the initial amount present, whereas the release of vancomycin was in the range 0.8%-3.3%. The release kinetics showed a similar pattern for both drugs. After a high initial release of drug, a reduced, but constant, elution was observed over the next few days. CONCLUSIONS: The delivery of gentamicin and vancomycin from PMMA cement was high initially, with sustained release over several months. Incorporation of vancomycin into the surface of the spacers permitted spacers to be prepared with multiple antibiotics present and without adversely affecting the release kinetics of the agents. The gentamicin-vancomycin combination shows potential for the treatment of infection following total hip replacement in specific patients.

**Key Quote** – “The superficial application of vancomycin using the ‘surface drill hole’ technique eliminates the problem of interference between release of gentamicin and vancomycin from PMMA cement. Moreover, the concentrations of gentamicin (1.9%) and superficial vancomycin (2.5%) enabled us to obtain an optimal ratio (1:1) in this elution system.” (p. 332)

**Exactech Literature # 002I**

**PRE-FORMED ARTICULATING KNEE SPACER IN TWO-STAGE REVISION FOR THE INFECTED TOTAL KNEE ARTHROPLASTY**


**Abstract** – We performed a prospective study to assess safety and effectiveness of a pre-formed articulating spacer made of gentamicin-impregnated acrylic cement in the management of infected total knee arthroplasty. Twenty-one consecutive patients with unilateral deep infection were treated by two-stage revision in two centres. Two patients were excluded, and 19 patients remained available for assessment. The mean implantation time of the spacer was 12 weeks. The rehabilitation programme between stages consisted in early range of motion exercises and partial weight bearing. Mean follow-up after removal of the spacer and insertion of the final prosthesis was 24 (range, 12-43) months. No patient had recurrence of infection at the latest follow-up. The mean Knee Society functional score during spacer management was rated 75 points and was rated 84 points at the latest follow-up. No device-related complication was observed.

**Key Quote** – “Unfortunately, cement spacers moulded in the operating theatre do not have reproducible mechanical characteristics, and there is a potential risk fracture of the components…Scott used a spacer prosthesis in combination with antibiotic-impregnated cement chains. A major drawback of the spacer prosthesis is the presence of hardware, which could theoretically favour bacterial adhesion.” (Discussion)

**Exactech Literature # 003I**

**STRATEGIES AND RESULTS OF TWO-STAGE TREATMENT FOR THE INFECTED THA AND TKA**

Meani E, Castelli C. Poster presented at the American Academy of Orthopaedic Surgeons Meeting; 2006 March 22-26; Chicago, IL.

**Key Quote** – TKA block spacer disadvantages “Stage 1: pain, difficult mobility, knee instability and bone loss. Stage 2: scar formation, shortening of the extensor mechanism, retraction of the joint capsule and ligaments and more constrained implant.”

**Exactech Literature # 005I**
**Aseptic Versus Septic Total Hip Arthroplasty Revision: Comparing the Results**

Romano Cl, Romano D, Logoluso N, Meani E. Poster presented at the 76th Annual American Academy of Orthopaedic Surgeons Meeting; 2009 Feb 25-28; Las Vegas, NV.

**Introduction** – Two-stage re-implantation using an interval spacer of antibiotic-impregnated bone cement is a well-established and accepted method of treatment for chronic infection of total hip prosthesis with eradication rates exceeding 90 percent in most series.

However, little data is currently available on medium-term results and functional outcome of two-stage revision surgery for chronically infected hip prosthesis compared to aseptic one-stage revision. Preformed articulating antibiotic-loaded spacers provide predictable mechanical resistance and antibiotic elution rates while long step spacers allow the surgeon to overcome the frequent proximal bone loss at the femoral level.

The purpose of this study was to evaluate the medium-term results of aseptic versus two-stage septic hip revision, performed according to a standardized and reproducible treatment protocol.

**Key Quote** – “Two-stage revisions for infected hip prosthesis using a preformed antibiotic-loaded cement spacer (InterSpace Hip) and uncemented revision prosthesis offers medium-term success rates equivalent to one-stage non-infected revisions.” (Conclusion)

**Treatments of Gelenohumeral Sepsis With a Commercially Produced Antibiotic-Impregnated Cement Spaccer**


**Abstract** – BACKGROUND: We report our experience in treating infected shoulder arthroplasty and primary shoulder sepsis using a commercially produced antibiotic-impregnated cement spacer. MATERIALS AND METHODS: We treated 16 shoulders in 15 patients for infected arthroplasty or osteomyelitis of the proximal humerus with irrigation and débridement, hardware removal, or humeral head resection, or both, and placement of an interval articulating hemiarthroplasty with a commercially made gentamicin-impregnated cement spacer. RESULTS: Mean follow-up was 20.5 months after spacer placement. At the time of débridement, 12 shoulders had positive cultures; the most common organisms were methicillin-resistant Staphylococcus aureus (n = 3) and S. epidermidis (n = 3). Twelve patients underwent revision. Four refused revision and have retained antibiotic spacers. White blood cell counts returned to within normal ranges in all patients at the time of revision, the erythrocyte sedimentation rate was 5 in 12 patients, C-reactive protein in 8 of 12 patients, and interleukin-6 in 9 of 11 patients. Mean visual analog pain scale score decreased from 8.4 before spacer placement to 0.5 at the final follow-up. Active forward flexion increased from a mean of 65 degrees to 110 degrees, and active external rotation from -5 degrees to 20 degrees. Mean University of California Los Angeles (UCLA) Shoulder Rating Scale score increased from 7 to 26, Simple Shoulder Test (SST) from 1.2 to 6.6, American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form score from 16 to 74, and Constant score from 16 to 57. There was no recurrence of infection. CONCLUSIONS: Treatment of glenohumeral sepsis with a commercially produced antibiotic-impregnated cement spacer appears to be an effective treatment modality, and serum interleukin-6 level appears to be useful in the evaluation of shoulder infection.

**Key Quote** – “A commercially produced spacer may be as effective in controlling infection as an intra-operatively crafted spacer because it allows for a more predictable level of antibiotic elution, eliminates the operating room time required for crafting the spacer on the back table, has a smooth articular surface, and may allow better shoulder function than intra-operatively produce spacer implants.” (Conclusions p. 5)

**Measurements of In Vivo Intra-Articular Gentamicin Levels from Antibiotic Loaded Articulating Spacers in Revision Total Knee Replacement**


**Abstract** – Previous in vitro studies have found high levels of antibiotic release in the days immediately following implantation of antibiotic loaded articulating spacers. However there are relatively few data describing the elution profile beyond this immediate period. This study was designed to measure if gentamicin levels continue to be clinically therapeutic after an extended period following in vivo implantation. Twelve patients received a gentamicin loaded articulating spacer between a 1st and 2nd stage revision total knee arthroplasty. At the 2nd stage procedure synovial fluid and blood samples were collected and assayed for the presence of gentamicin. The second stage revision occurred at a median of 99 days following spacer insertion. The median intra-articular gentamicin levels were 0.46 mg/L (0.24 to 2.36 mg/L) which would be considered therapeutic. There were no cases of reinfection. In this study, preformed articulating spacers containing gentamicin provided therapeutic concentrations in the synovial fluid surrounding the joint throughout the period of implantation. These data confirm the observations from in vitro studies, where a prolonged elution profile was observed for such spacers.

**Key Quote** – “In this study, preformed articulating spacers containing gentamicin provided therapeutic concentrations in the synovial fluid surrounding the joint throughout the period of implantation.”

**Exactech Literature # 012I**

**Exactech Literature # 009I**

**Static and Mobile Antibiotic-Impregnated Cement Spacers for the Management of Prosthetic Joint Infection**


**Abstract** – Two-stage treatment is currently the most common approach for management of an infected joint prosthesis in the United States. Static antibiotic-impregnated polymethylmethacrylate cement spacers have traditionally been used; increasingly, however, mobile or articulating spacers are being utilized. Advocates of mobile spacers have cited potential advantages, including more reproducible treatment protocol.

**Key Quote** – “Despite the relatively low dose of antibiotic, ... the eradication of prosthetic joint infections indicated that none of 21 patients treated with the preformed articulating spacer became reinfeected at a mean follow-up of 2 years.” (p. 360)

**Exactech Literature # 013I**

**Comparing the Results**

Las Vegas, NV.

**Key Quote** – “In this study, preformed articulating spacers containing gentamicin provided therapeutic concentrations in the synovial fluid surrounding the joint throughout the period of implantation.”

**Exactech Literature # 012I**

**TREATMENT OF GLENOHUMERAL SEPSIS WITH A COMMERCIALLY PRODUCED ANTIBIOTIC-IMPREGNATED CEMENT SPACER**

**Measurements of In Vivo Intra-Articular Gentamicin Levels from Antibiotic Loaded Articulating Spacers in Revision Total Knee Replacement**

**Key Quote** – “A commercially produced spacer may be as effective in controlling infection as an intra-operatively crafted spacer because it allows for a more predictable level of antibiotic elution, eliminates the operating room time required for crafting the spacer on the back table, has a smooth articular surface, and may allow better shoulder function than intra-operatively produce spacer implants.” (Conclusions p. 5)

**Exactech Literature # 013I**
PREFORMED GENTAMICIN SPACERS IN TWO-STAGE REVISION HIP ARTHROPLASTY: FUNCTIONAL RESULTS AND COMPLICATIONS


Abstract – Two-stage revisions with antibiotic-loaded spacers have gained popularity for treating infected hip joint arthroplasties. The aim of this prospective study was to assess patient functionality between stages and treatment impact on duration of hospital stay and to describe related complications. Sixty-one consecutive patients with infected hip arthroplasties underwent two stage revision with preformed spacer implantation. Mean Harris Hip and Merle d’Aubigné scores between the two stages were 39.9 and 7.6, respectively. Forty-six patients (75.4%) were able to leave hospital between stages. Spacer dislocation occurred in 16.4%. No cases of spacer breakage were noted. Preformed cement spacers provide acceptable functional outcome between revision hip arthroplasty stages and facilitate the surgical procedure without increasing mechanical complication rates.

Key Quotes – “Preformed cement spacers provide acceptable functional outcome between revision hip arthroplasty stages and facilitate the surgical procedure without increasing mechanical complication rates.” (Abstract)

“An important finding in our series was the absence of spacer fractures.” (Discussion)

Exactech Literature # 014I

TWO-STAGE REVISION SURGERY WITH PREFORMED SPACERS AND CEMENTLESS IMPLANTS FOR SEPTIC HIP ARTHRITIS: A PROSPECTIVE, NON-RANDOMIZED COHORT STUDY


Abstract – Outcome data on two-stage revision surgery for deep infection after septic hip arthritis are limited and inconsistent. This study presents the medium-term results of a new, standardized two-stage arthroplasty with preformed hip spacers and cementless implants in a consecutive series of adult patients with septic arthritis of the hip treated according to a same protocol.

Key Quotes – “The most relevant clinical advantage of using an antibiotic-loaded spacer is that it helps to maintain joint space and minimizes the risk of large limb shortening, while local antibiotic delivery prevents bacterial re-colonization of the implant. Furthermore, preformed antibiotic-loaded spacers offer off-the-shelf availability, a standardized and reproducible technique, known mechanical resistance predictable antibiotic release and shorter operating time, being available in short and long stemmed shapes that can be chosen intraoperatively based on femoral bone loss.” (Discussion)

“Satisfactory outcomes can be obtained with two-stage revision hip arthroplasty using preformed spacers and cementless implants for prosthetic hip joint infections of various etiologies.” (Conclusion)

Exactech Literature # 015I