CAN WE IMPROVE PROTOCOLS IN CLINICAL PRACTICE?

35th Annual meeting of the European Bone and Joint Infection Society

Heraeus Medical satellite symposium

September 2nd, 2016, 12:40–13:40
Oxford, United Kingdom
INTRODUCTION

Infection has been a persistent problem throughout the history of surgery, including orthopaedics. While the development over the years of improved surgical techniques, antibiotics and methods of antimicrobial delivery have reduced infection rates, new challenges have emerged, including multi-drug resistance and biofilms.

At the satellite symposium sponsored by Heraeus Medical at the 35th annual meeting of the European Bone and Joint Infection Society (EBJIS), three experts in septic bone and joint surgery discussed current knowledge of biofilms and local methods of overcoming the challenge of infection in orthopaedic surgery. The multi-disciplinary panel of speakers was comprised of Prof. Carlo Romanò, Prof. Lorenzo Drago and Mr Mike Reed.

Highlights and key points from their presentations are presented in this report.

WHAT IS “BIOFILM-RELATED IMPLANT MALFUNCTION”?

Prof. Carlo Romanò said that a new understanding of these microbial communities is driving a revolution that may transform the science of microbiology. Orthopaedics is not unique in facing the challenge of biofilms. They affect fields as diverse as the food and beverage industry, water processing and marine engineering. In industry, Flemming (2002) introduced the concept of the ‘threshold of interference’ i.e. the level of accumulation of biofilm that leads to observable and detrimental effects. In orthopaedics this means that bacteria may be colonising a surface for months or years but be undetected before reaching the level at which they trigger an immune response and signs of infection. But in the absence of an immune response there may still be bacterial accumulation, leading to low grade infection and symptoms such as persistent pain, stiffness, lack of range-of-movement, fibrosis, ‘aseptic’ implant loosening and non-union of fractures.

AVOIDING FALSE NEGATIVES AND POSITIVES IN BIOFILM-ASSOCIATED INFECTIONS

Improving detection of biofilms is key, as false positives and negatives can cloud the picture. For example, Staphylococcus aureus may exist in synovial fluid as aggregates which cannot be cultured. To reduce false positives, the use of clean instruments and gloves when retrieving implants or tissue samples and closed systems are essential. False negatives arise because of the seclusion of bacteria within the biofilm. This can be overcome by disruption of the biofilm with techniques such as sonication for implants, and treatment of tissue samples with dithiothreitol (DTT) to release bacteria for culture.

A weak imbalance, in which bacteria induce an implant malfunction, without a relevant clinical impact
BIOFILMS AND ANTI-BIOFILM STRATEGIES

Prof. Lorenzo Drago described how local strategies can address some of the key issues relating to biofilms in orthopaedics. A mature biofilm can form within 24 hours of contact with an implant and can actually penetrate the surface of titanium. The matrix of biofilms is more abundant than the bacteria themselves and must be disrupted in order to expose the organisms to antimicrobial agents.

Biofilms are also not all the same. As well as differing by organism e.g. between Gram-positive and negative bacteria, they differ according to the age, or stage, of the infection (early, delayed or chronic).

Some organisms are more pathogenic because they produce more biofilm e.g. *Pseudomonas aeruginosa* and *S. aureus* produce acute infections and are high biofilm producers whereas *Propionibacterium acnes* is a low biofilm producer.

Multi-drug resistance may also be related to biofilm formation. For example, methicillin-resistant *S. aureus* (MRSA) produces more biofilm than methicillin-susceptible *S. aureus* (MSSA). Since antibiotic resistance is associated with increased costs, suffering, and mortality, biofilms can be responsible for magnifying these issues.

FUTURE AND CURRENT LOCAL ANTI-BIOFILM STRATEGIES

Approaches to preventing the formation of biofilms include modifying the implant surface with lasers to prevent adhesion, which has proved successful in dentistry. Coating implants also has potential to prevent adhesion; gentamicin plus clindamycin has shown good results. Palmitate coating reduces the adhesion index of *S. aureus* on polythene and titanium and the index is reduced further when gentamicin is added.

Antibiotic-loaded materials, such as cements, are available: with vancomycin, gentamicin and clindamycin. Their potential drawback is the development of resistance but antibiotics in cements are for prevention of infection: not to treat it. Also, they provide antibiotic concentrations which are much higher than the Minimum Inhibitory Concentrations of commonly-infecting bacteria. In addition, the maximum plasma concentrations are too low to induce resistance. As well as developing new strategies and techniques we must learn to make the best use of existing measures such as cements.

Phases of biofilm development: (1) and (2) Bacteria adhere to the implant surface, (3) and (4) Proliferation of bacteria and maturation of biofilm. (5) Disassembly of sections of biofilm and release of bacteria.
CLINICAL IMPACT OF LOCAL ANTIBIOTIC STRATEGIES IN PREVENTION OF PERI-PROSTHETIC JOINT INFECTIONS

Mike Reed discussed his experience of optimising local antibiotic use to reduce peri-prosthetic joint infections (PJIs). He had investigated two different approaches: nasal decolonisation of S. aureus and the use of antibiotic-loaded bone cement.

*S. aureus* is a significant cause of infections common to total hip and knee replacement (THR and TKR) and fractured neck of femur (FNOF). Treatment of nasal carriage of *S. aureus* has been shown to reduce surgical site infections (SSIs) by almost 60% and reduce hospital stay, leading to a new study of the effect in orthopaedics. In his institution’s series of over 12,000 patients, nasal decolonisation of MSSA carriers had a dramatic effect in reducing MSSA and “all infections”. The effect was most dramatic in THR for reasons which are not currently clear.

SUPERIOR OUTCOME IN HIP AND KNEE ARTHROPLASTY THROUGH ANTIBIOTIC LOADED BONE CEMENTS (ALBC)

The benefits of bone cements such as PALACOS®R+G (with gentamicin) are well-documented and accepted in THR, but what about TKR? Registry data show that significantly fewer revisions are required when PALACOS®R+G has been used, compared to all other bone cements. It is also worth noting that PALACOS®R+G (with gentamicin) significantly outperforms plain PALACOS®.

SIGNIFICANT REDUCTION OF SSI THROUGH DUAL ANTIBIOTIC LOADED BONE CEMENTS

It is particularly important to optimise strategies for the reduction of PJIs in high risk patients. So which bone cement best overcomes current challenges in PJI prevention, such as biofilm formation, in high risk patients? Encouraged by data showing that COPAL®G+C bone cement is more effective in preventing biofilm formation than PALACOS®R+G, a new quasi-randomised, double-blind study of the two bone cements in patients requiring hemiarthroplasty for a fractured neck of femur was carried out. There was a significant reduction in deep and superficial SSIs with COPAL®G+C compared with PALACOS®R+G. Reduction in superficial SSIs was explained by the previously-observed presence of high antibiotic concentrations in wound fluid. Extrapolation of the reduction in infection rates to the entire UK hip hemiarthroplasty population, would lead to healthcare savings of over £4m.
DUAL ANTIBIOTIC LOADED BONE CEMENTS DOES NOT AFFECT ANTIBIOTIC RESISTANCE PROFILES

A concern regarding the use of antibiotic-loaded bone cements is whether they cause antibiotic resistance. In this study there were no significant differences in resistance between PALACOS®R+G and COPAL®G+C. The only cases of resistance with COPAL®G+C were to gentamicin and clindamycin, which is as expected. Resistance to other standard antibiotics, including teicoplanin, vancomycin, daptomycin, linezolid and rifampicin, remained low. Furthermore, COPAL®G+C completely eradicated infection caused by Corynebacterium species and S. aureus. The study investigators considered that the benefit in terms of reduced PJI far outweighed the risk of development of bacterial resistance and supports their continued use of COPAL®G+C in high risk patients requiring hip hemiarthroplasty for fractured neck of femur.

<table>
<thead>
<tr>
<th>Northumbria Healthcare Trust</th>
<th>Low dose single antibiotic cement</th>
<th>High dose dual antibiotic cement</th>
<th>Chi squared test</th>
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<tbody>
<tr>
<td>1941 hemiarthroplastics</td>
<td>681</td>
<td>1260</td>
<td></td>
</tr>
<tr>
<td>Deep infections</td>
<td>21 (3.1 %)</td>
<td>15 (1.2 %)</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Resistant to clindamycin</td>
<td>14 (2.1 %)</td>
<td>15 (1.2 %)</td>
<td>p=0.134</td>
</tr>
<tr>
<td>Resistant to gentamicin</td>
<td>10 (1.5 %)</td>
<td>12 (1.0 %)</td>
<td>p=0.305</td>
</tr>
<tr>
<td>Resistant to both</td>
<td>8 (1.2 %)</td>
<td>12 (1.0 %)</td>
<td>p=0.643</td>
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SUMMARY

The prevention of PJIs is vital for reducing suffering to patients and also to reduce healthcare costs. Current protocols in this area possibly do not adequately address all the issues involved in this challenge. For example, they may not differentiate between prevention and treatment of infections or consider measures to overcome biofilms and the special needs of high risk patients. The presentations in this symposium have discussed ways in which protocols for PJI infection could be improved:

- Understanding biofilms is an essential aspect of reducing PJIs
- The association of biofilms with multi-drug resistance and pathogenicity emphasises the need for anti-biofilm strategies
- Future approaches may require specific anti-biofilm strategies that focus on the prevention of microbial adhesion to the implant surface
- Current strategies show that local antibiotic delivery is effective in reducing PJIs
- Antibiotic-loaded bone cement (PALACOS®R+G) reduces infection rates in both THR and TKR compared with plain cements
- COPAL®G+C reduces PJIs in high risk arthroplasty patients without increasing resistance, compared with PALACOS®R+G
ABOUT OUR SPEAKERS

Carlo L. Romanò, MD
ISTITUTO ORTOPEDICO GALEAZZI IRCCS, MILANO, ITALY

Prof. Carlo Romanò is Director of the Centre for Reconstructive Surgery and Bone and Joint Infections and co-Director of the “Milano Biofilm Centre” at the IRCCS Orthopaedic Institute Galeazzi, Milan, Italy.

His clinical and research interests focus on the prevention, diagnosis, and treatment of bone and joint infections, particularly within prosthetic surgery, local antibiotic therapy, anti-biofilm technologies and biomaterials.

Co-founder and past-President of the Italian Study Group on Osteo-articular Infections (GISTIO), he served as President of the European Bone and Joint Infection Society (EBJIS) and received the “Best Research” and “Very Promising Research” EBJIS Awards in 2010 and 2013.

Lorenzo Drago, PhD
ISTITUTO ORTOPEDICO GALEAZZI IRCCS, MILANO, ITALY

Prof. Lorenzo Drago is currently Head of Laboratory Analysis at IRCCS Galeazzi Orthopaedic Institute in Milan, Italy.

A key research interest is biofilm formation and anti-biofilm agents, as well as investigating new methods in analytical molecular biology to study microorganisms and host-parasite interactions. He has over 170 peer reviewed publications and in 2013 his research was awarded the European Bone and Joint Infection Society (EBJIS) “Very Promising Research” award.

Mr Mike Reed, MD
NORTHUMBRIA NHS HEALTHCARE FOUNDATION TRUST, UK

Mr Reed is a consultant trauma and orthopaedic surgeon with the Northumbria NHS Healthcare Foundation Trust, a position that he has held since 2003. He specialises in trauma, and hip and knee arthritides including revision joint replacements.

Mr Reed’s research interests are focused on clinical outcomes and infection prevention, diagnosis and management. For example he is lead investigator on numerous randomised controlled trials, including a recent study assessing the impact of high dose antibiotic-loaded cements on infection prevention following hip fracture surgery.
REFERENCES


PROVIDING A PLATFORM FOR DISCUSSING HOW TO TACKLE THE CHALLENGES OF BIOFILM RELATED INFECTIONS

Heraeus Medical have a history of promoting discussion to better understand the underlying causes of biofilm related prosthetic joint infection; recognising important topics ahead of the field. Heraeus are noted for facilitating the open sharing of innovative ideas by bringing together renowned experts in satellite symposia at national and international meetings.

KEY HERAEUS MEDICAL-SPONSORED SYMPOSIA:

2010: Local antibiotics
- Aseptic Surgery Forum (ASF), Paris: Local antibiotics in arthroplasty – benefit or risk?

2011: Role of biofilm
- European Bone and Joint Infection Society (EBJIS), Copenhagen: Fighting biofilm – Today and tomorrow

2012: Importance of managing prosthetic joint infection
- EBJIS, Montreux: Infection management – ensuring best patient care
- Deutscher Kongress für Orthopädie und Unfallchirurgie (DKOU), Berlin: Prevention of PJI – in Primary and revision arthroplasty

2013: Antibiotic concepts as a prophylaxis against infection
- Swiss Society for Orthopaedics and Traumatology (SGOT), Lausanne: The most common errors in management of perioperative joint infections
- EBJIS, Prague: Antibiotics in infection prevention – ways to increase efficacy
- DKOU, Berlin: Success factors in septic surgery
- Società Ligure Piemontese Lombarda di Ortopedia e Traumatologia (SPLLOT), Milan: International consensus on prosthetic joint infection

2014: Infection management
- Norddeutsche Orthopäden- und Unfallchirurgen Vereinigung (NOUV), Berlin: Infection Management – Role of antibiotic loaded bone cement
- SGOT, St. Gallen: Factors of success for infection management – diagnosis, treatment, teamwork
- EBJIS, Utrecht: Infection management – building bridges from PJI to posttraumatic infections
- DKOU, Berlin: The infected knee arthroplasty – how to detect and treat?

2015: Tailoring antibiotic prophylaxis in high risk patients
- European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Prague: Infection in high risk patients: Can we improve?
- British Orthopaedic Society (BOA), Liverpool: Infection in the high risk arthroplasty patient
- DKOU, Berlin: Infections in the high risk arthroplasty patient

2016: Biofilm as a driver of infection
- EFORT, Geneva: Do you know the Drivers of infection prevention?
- EBJIS, Oxford: Anti-biofilm strategies – what is effective?
GOOD-TO-KNOW ABOUT ANTIBIOTIC-LOADED ACRYLIC CEMENT

WHY USE ANTIBIOTIC-LOADED CEMENTS?
- Acrylic cement, or poly-methyl-methacrylate (PMMA), is a polymer-based material used for the fixation of joint implants to bone
- Antibiotic-loaded bone cement functions as a prophylaxis and is an important aid in the prevention of prosthetic infections\(^6,12\)
- Addition of gentamicin to bone cement markedly reduces bacterial adherence, as compared to unloaded bone cement;\(^13\) and bone cement loaded with clindamycin plus gentamicin (COPAL\(^\text{R}\)+G+C) is more effective in preventing biofilm formation than bone cement with gentamicin only;\(^3,15\)
- Cements loaded with a low dose of antibiotic (≤ 1 g of antibiotic per batch of cement) and those with a high dose of antibiotic (> 1 g antibiotic per batch of cement) are indicated for prophylaxis and supporting treatment by prophylaxis against biofilm formation respectively\(^6\)
- High-dose dual antibiotic-loaded cement significantly reduces surgical site infection rate after hip hemiarthroplasty in high risk patients, as compared to standard low-dose antibiotic-impregnated cement\(^14\)
- Best results are obtained when antibiotic prophylaxis is used both locally and systemically\(^6\)

HOW ARE ANTIBIOTICS RELEASED FROM THE CEMENT?
- Antibiotics are released from the bone cement by diffusion\(^13\)
- There are significant differences in the manner that different PMMA cement brands release gentamicin, due to different hydrophilic properties of the bone cement matrix\(^9\)
- The antibiotic is released in two stages: an initial high, concentrated rapid release followed by slow diffusion from the cement surface over a longer period;\(^13\) the unique composition and ingredients of PALACOS\(^\text{R}\)+G bone cement allow for unique antibiotic release rates\(^15\)
- The initial high dose of antibiotic coincides with the period when risk of infection is at its highest
- Because of the localised drug delivery the systemic burden for the patient is very low, even when using high-dose antibiotic-loaded cement, therefore undesirable toxic effects are unlikely\(^13\)

ANTIBIOTIC SELECTION
- A good choice of antibiotic is one with a broad spectrum of activity and a low percentage of resistant species such as gentamicin;\(^14\)
  - the antibiotic needs to be heat resistant to withstand the temperature rise during cement polymerisation\(^13,14\)
- A suitable elution profile enables release of the antibiotic from the cement, elution is also facilitated by the addition of a second antibiotic (synergistic effect)\(^6,14\)

SHOULD ANTIBIOTIC RESISTANCE BE OF CONCERN?
- No direct evidence links bacterial resistance to routine use of antibiotic-loaded bone cement as a prophylaxis in primary arthroplasty\(^2\)
- Swedish registry data show that while use of antibiotic-loaded bone cement is high in the country (used as a prophylaxis in 95% of revision hip or knee arthroplasty procedures and 85% of primary joint replacement), the emergence of resistant strains of organisms is minimal\(^9\)
- Furthermore, a large cohort study in North America found antibiotic-loaded bone cement to be associated with both reduced antibiotic resistance and reduced infection in comparison to control groups\(^8\)
RECOMMENDED READING


2. Kendoff DO, Gehreke T, et al., Bioavailability of gentamicin and vancomycin released from an antibiotic containing bone cement in patients undergoing a septic one-stage total hip arthroplasty (THA) revision: a monocentric open clinical trial. Hip Int 2016;26(1):90-6. An open clinical trial evaluating bioavailability of gentamicin and vancomycin loaded bone cement (COPAL®G+V). Both antibiotics were absorbed slowly and reached plasma concentrations below toxic levels; the bone cement was efficacious and well-tolerated among patients undergoing total hip arthroplasty


5. F.Jensen C, Gupta S, Sprowson A, et al., High dose, double antibiotic-impregnated cement reduces surgical site infections (SSI) in hip hemiarthroplasty: A randomised controlled trial of 848 patients with intracapsular neck of femur fractures. Bone Joint J 2013;95-B(SUPP 31), 53. A randomised controlled trial of high risk patients showing a 3.3 % lower risk for total SSI in COPAL®G+C treated patients compared to the PALACOS®G+C group; COPAL®G+C may be recommended for patients with high risk of periprosthetic infection undergoing primary hip hemiarthroplasty

6. Meyer J, Piller G, Spiegel C, et al., Vacuum-Mixing Significantly Changes Antibiotic Elution Characteristics of Commercially Available Antibiotic-Impregnated Bone Cements. J Bone Joint Surg 2011; 93: 2049–56. Among six antibiotic-laden cements, PALACOS®R+G together with Cobalt G-HV produced antimicrobial activity, which was significantly greater than that of all other products; and only vacuum-mixed PALACOS®R+G remained at or above the susceptibility threshold for all five days of the elution assay

7. Fevang BTS, Lie SA, Havelin LI, et al., Improved results of primary total hip replacement - Results from the Norwegian Arthroplasty Register, 1987–2007 Acta Orthopaedica 2010;81(6): 649–659. Patients with cemented Charnley prostheses – with PALACOS® (or Simplex cement) – had a better overall survival compared to those with uncemented, hybrid, inverse hybrid, and non-Charnley cemented prostheses

8. Ensing GT, van Horn JR, van der Mei HC, et al., COPAL® bone cement is more effective in preventing biofilm formation than PALACOS®R+G. Clin Orthop Relat Res 2008;466(6):1492–8. A research article showing that bone cement containing clindamycin plus gentamicin (COPAL®G+C) had more extensive antibiotic release and more effectively decreased biofilm formation compared to bone cement with gentamicin only (PALACOS®R+G)


12. Furnes O, Espehaug B, Havelin LI. Which cement should we choose for primary THA? In: The well-cemented total hip arthroplasty. Theory and Practice. Breusch SJ, Malchau H, editors. Heidelberg, Germany: Springer Medizin Verlag 2005: 103–106. Cement type may be a more important predictor for long-term outcome than commonly used prosthesis brands; PALACOS® (and Simplex cements) are associated with the lowest revision risk

13. Squire MW, Ludwig BJ, Thompson JR et al., Premixed Antibiotic Bone Cement – An In Vitro Comparison of Antimicrobial Efficacy. J Arthroplasty 2008;23(6 Suppl. 1). High viscosity bone cements like PALACOS® demonstrated a trend of superiority or were significantly superior with respect to bacterial growth inhibition when compared to the lower viscosity products
14. Frommelt L. Local Antibiotic Therapy. In: Lokale Antibiotikatherapie in Septische Knochenchirurgie. Schnettler and Steinau, editors. Georg Thieme Verlag. 2004; 82-90(5); ISBN: 978-3131169815. Article discussing why antibiotic-loaded bone cement should be used and when; the properties of antibiotic loaded bone cements and rules for their use; the properties of antibiotics and their release behaviour; and the use of antibiotic-loaded bone cement and resistances.

