Antibiotic Coated Implants in the Management of Risk Patients

Development and Implementation

Andrea Montali
Head of R&D Biomaterials EU
Synthes GmbH
Oberdorf, Switzerland
Intramedullary Tibial Nail

Titanium alloy implant for the operative treatment of fractures in the tibial shaft as well as for metaphyseal and certain intraarticular fractures of the tibial head and the pilon tibiale.

Implant is inserted into the medullary canal of the tibia from proximal side (i.e. the knee)

Images courtesy of Prof. M. Raschke, Universitätsklinikum Münster
Systemic perioperative antibiotic prophylaxis – The standard of care in surgeries involving surgical incisions and implantation of a foreign body. Efficacy proven*
Bacterial implant colonization

• Bacteria colonize the implant surface
• Bacteria may produce a protective **biofilm, which shields** them against the **immune system** as well as against the effect of **antibiotics**
• These circumstances can lead to **implant related infection**.
• In **75% of all infections** the causative bacteria grow in biofilms
Why an antibiotic coating?

The clinical problem:

Bacterial Colonization

Implant colonization by bacteria can cause implant related infection

Implant colonization is more likely:

• During implantation
• In open / contaminated fractures
• Previous infections
• Revision procedures

Harris et al., Injury, 2006

Image courtesy of Prof. M. Raschke, Universitätsklinikum Münster
Coated IM Nail / Biointerface 2012 / A. Montali

Reduce or avoid bacterial colonization

Coating of Tibial Nail with a layer of antibiotic laden polymer

• **Fully resorbable coating**
  - Matrix (carrier): poly-lactide
  - Antibiotic: Gentamicin sulphate

• **Release** of the antibiotic immediately after implantation

→ Achieve **very high** local concentrations **immediately** after implantation

1. PROtect antibiotic coating
2. Coated medical device
3. Bacteria
4. Dead bacteria
Why an antibiotic coating?

Surgical fracture treatment with an antibiotic coated implant:

- Point of care delivery of active substance
- High local concentration without systemic side-effects
- Reduced dosage required
- Combined action of implant and active substance
- Surgical technique remains unchanged
Primary Mode of Action – the implant:

• Fracture fixation
  → Mechanical properties and handling of coated nail no different than handling of an uncoated nail

Ancillary Action – the coating:

• Coating effective against bacteria most commonly encountered in bone infections and contaminated fractures

Other Requirements:

• Coating is abrasion resistant
• Coating does not affect fracture healing
• Bactericidal level of antibiotic is reached in immediate vicinity of implant within minutes after implantation
Preclinical testing – *in vivo*

Rat tibia infection model

- Inoculate with *Staph. Aureus*
- Place pin with and without antibiotic coating in intramedullary canal
- Evaluate occurrence of infection, implant colonization and tissue histology at 42 days implantation

Results

No inflammatory reactions or other adverse events after 6 weeks of implantation test group

No clinical, radiological or histological signs of infection in test group

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Lucke et al., Bone, 2003
Rabbit femoral implant – Colonization Study

- Inoculate with *Staph. Aureus*
- Place pin with and without antibiotic coating in intramedullary canal
- Evaluate implant colonization and tissue bacteria counts

**Results**

Reduced colonization of implant by bacteria in test group at 7 and 14 days of implantation
Sheep Tibial Osteotomy – Colonization Study

Objectives:

- Demonstrate the efficacy and safety of the gentamicin coating in a relevant large animal fracture model
- Demonstrate reduced bacterial colonization
- Local and systemic gentamicin levels

Experimental Design:

- Unilateral midshaft tibial osteotomy in sheep
- Stabilized with either coated or uncoated Humeral IM Nail
- Multiple inoculation levels with *Staph Aureus*
- 7 day time point
Sheep Tibial Osteotomy – Colonization Study

Results:

• Reduced colonization of implant by bacteria in test group at 7 days of implantation
• No detectable systemic antibiotic levels
## Pre-clinical Data – Animal Studies - Overview

<table>
<thead>
<tr>
<th>Model</th>
<th>CFU</th>
<th>Duration</th>
<th>Outcome</th>
<th>Group</th>
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<td>$10^3$</td>
<td>42 days</td>
<td>Prove efficacy</td>
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<tr>
<td>Sheep tibia colonization</td>
<td>$10^4$, $10^6$, $10^8$</td>
<td>7 days</td>
<td>Colonization, concentration local, systemic</td>
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Summary and Conclusions *in vivo* Studies

- PDLLA coating with gentamicin is effective at preventing bacterial colonization of implant surfaces and bone tissue in challenging animal models.
- Coating does not appear to result in appreciable systemic exposure.
- Gentamicin appears to be near completely gone after 7 days.
- Likely does not result in increased antibiotic resistance.

In all performed *in vivo* studies at various institutions the coated implants NEVER failed when challenged in a prophylaxis model.

Safety and efficacy proven *in vitro* and *in vivo*.
Clinical history

Expert TN PROtect:
• CE marked in January 2011
• Full launch in May 2011
• More than 500 successful implantations to date

Ongoing:
• Prospective open label post market clinical follow-up to evaluate clinical usefulness of the Expert TN PROtect
• Enrollment of 100 patients concluded in March 2012
Universitätsklinikum Münster: Prof. M. Raschke, Dr. T. Fuchs

Date of accident: 25.03.2011

Case history: Accident with an industrial press

Diagnosis: lower right leg fracture: Gustillo IIIA open, AO 42 B1 - suspicion of vascular injury
penetrating chest injury left side
subclavia-dissection left side with thrombus

Surgical treatment

25.03.2011: thoracotomy
partial pneumonectomy left side
external fixator lower right leg
soft tissue treatment

11.04.2011: procedural change external to internal fixation 17 days after initial treatment
removal external fixator → Expert TN PROtect (10x390)
Clinical history – Exemplary Case

pre-OP

post-OP – Ex Fix
Clinical history – Exemplary Case

Procedural change:
pre-OP planning

Procedural change:
post-OP IM fixation
Clinical history – Exemplary Case

6 month follow – up:
Full weight bearing
Soft tissues healed
Consolidation of fracture far progressed
Normal mobility
Back to work, full time
Main challenges in developing an antibiotic coated orthopedic implant:

1. Substantial preclinical testing
2. Process development & validation challenges
3. Lengthy discussions with regulatory agencies
4. Time and Cost
5. Proof of clinical efficacy extremely challenging using traditional statistical methods and clinical outcome measurements
# Acknowledgements

## Clinical / Scientific Partners

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<td>G. Schmidmaier</td>
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## Synthes Project Team

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<td>D. Boxem</td>
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<tr>
<td>F. Cirillo</td>
<td>H. Dietzler</td>
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<tr>
<td>A. Doherty</td>
<td>J. Dow</td>
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<td>S. Gasser</td>
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<td>A. Grüniger</td>
<td>E. Gruskin</td>
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<td>R. Harten</td>
<td>T. Kraemer</td>
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<td>M. Paris</td>
<td>C. Roth</td>
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<td>F. Schlottig</td>
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<td>T. Studer</td>
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<td>A. Waelchli</td>
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Thank you for your attention

Any questions?