The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study

Thomas Fuchs · Richard Stange · Gerhard Schmidmaier · Michael J. Raschke

Received: 20 December 2010 / Published online: 24 May 2011 © Springer-Verlag 2011

Abstract
Background The use of antibiotic-coated implants may reduce the rate of infection and facilitate fracture healing after surgical treatment of tibial shaft fractures. A new biodegradable gentamicin-loaded coating of an implant (UTN PROtect®) was CE-certified in August 2005. In this prospective, non-randomized case series, we investigated the clinical, laboratory and radiological outcomes of 21 patients who underwent surgical treatment in closed or open tibial fractures, as well as revisions with the UTN PROtect® gentamicin-coated intramedullary nail.

Methods Of 21 patients (13 men, 8 women), 19 completed the 6-month follow-up. The study population included patients with complex tibial fractures and late revision cases. Clinical outcomes comprised adverse events, including infections and the SF-36 physical score. Laboratory outcomes, including C-reactive protein and leukocyte count as inflammatory markers, haemoglobin and serum gentamicin, were measured at baseline and up to 6 months post operatively. Radiographic assessments of fracture healing and weight-bearing capacity were determined at 5 weeks, 3 and 6 months after surgery.

Results No implant-related infections occurred; one patient had superficial wound healing problems. Mean C-reactive protein levels remained below 5 mg/L throughout the study, with a peak at 4–7 days after surgery (4.4 mg/L; range 0.5–16.1 mg/L). Leukocyte counts and haemoglobin levels did not vary over time during the study. The mean SF-36 physical score at 6 months was 42.6 (range 19.4–56.7). Radiographic union defined as three or four bridged cortices was achieved in 11 patients (58%) after 6 months. The remaining eight patients showed partial fracture healing with one or two bridged cortices. Additionally, 13 patients (68%) demonstrated full weight-bearing capacity after 6 months.

Conclusions The use of the UTN PROtect® intramedullary nail was associated with good clinical, laboratory and radiological outcomes after 6 months. These preliminary results support the use of gentamicin-coated implants as a new potential treatment option for the prevention of infection in trauma patients and in revision cases.

Level of Evidence Level II.

Keywords Open fracture · Intramedullary nailing · Bone infection · Antibiotic coating · Osteomyelitis · Tibia · Soft tissue management

Introduction
Intramedullary nailing is the method of choice for treating tibial shaft fractures [16]. However, tibial fractures with severe soft-tissue damage that results in the loss of soft-tissue support and disrupted vascularity are especially prone to infection, non-union and other complications [4, 5]. Despite improvements in surgical techniques and the use of antibiotic therapy, deep wound infections and osteomyelitis remain serious complications that may lead to impaired healing, reduced limb function and lifethreatening septic conditions [20, 22].

Rates of infection associated with tibial fractures after surgical treatment vary depending on the severity of
fracture, soft tissue status and general patient condition [2, 7, 15, 16]. Overall infection rates are about 1–4% [2, 5]. Patients with open tibial fractures are at higher risk of infection, with rates ranging from 6 to 33% [3, 15–17]. Gaebler et al. [5] reported 13 infections (3.2%) among 467 patients after intramedullary tibial nailing, of which 5 (1.1%) were deep wound infections. Notably, 80% of all deep infections developed in Gustilo grade III open fractures [5]. Other studies have confirmed that the risk of deep wound infections increases with the severity of soft tissue injury by Gustilo type and fracture severity by AO type [7, 8, 15, 16].

Systemic prophylactic administration of antibiotics is accepted as standard practice to control bacterial contamination and prevent infection after surgery. In a review of seven clinical trials involving 913 patients with open limb fractures, perioperative administration of systemic antibiotics was associated with a 60% reduction in the relative risk (RR) of early wound infections compared with no prophylaxis or placebo (RR 0.41; 95% CI 0.27–0.63) [6]. Yet, a systematic review and meta-analysis of 22 trials involving 927 patients was inconclusive as to which systemic antibiotic provides the best protection against bone and joint infections [19].

Systemic antibiotics may have limited efficacy in decreasing the risk of infection associated with the use of foreign bodies such as prostheses and osteosynthetic devices [3, 17]. Bacteria can colonize the surface of an implant, forming a biofilm of an extracellular polysaccharide matrix (glycocalyx) that protects the bacteria from the antimicrobial action of systemic antibiotics. Furthermore, systemically delivered antibiotics might not reach the medullary canal of long bones when blood flow has been disrupted by trauma or intramedullary nailing [17]. Therefore, implant-related infection often requires aggressive treatment including removal of the implant, multiple revisions with surgical debridement and long-term antibiotic therapy [15, 16, 19].

To improve prophylaxis against implant-related infections, various systems have been developed for the local delivery of antibiotics at the tissue-implant interface. Gentamicin polymethylmethacrylate (PMMA) bead chains and gentamicin-coated collagen sponges (Sulmycin®; Septocoll®) can reduce the risk of infection directly at the site of the implant and its surrounding tissue [3, 9, 17]. However, PMMA beads must be removed after 4–6 weeks [3] and collagen sponges do not allow for continuous and controlled release of the antibiotic [4].

Alternatively, a polylactic acid (PLA) coating loaded with gentamicin offers both sustained release kinetics and biodegradability [4, 18]. Pre-clinical studies have shown the effectiveness of gentamicin-coated implants in preventing implant-related osteomyelitis even without systemic antibiotic prophylaxis [12, 17]. A new tibial titanium nail with a biodegradable gentamicin-loaded coating (UTN PROtect®, Synthes) was CE-certified in August 2005. In a pilot study of 8 patients with open tibial fractures treated with UTN PROtect® intramedullary nails, there were no infections within 1 year and all fractures healed within 6 months [17].

In this prospective, non-randomized case series, we investigated the use of the UTN PROtect® gentamicin-coated intramedullary tibial nail in the surgical treatment of closed and open tibial fractures and in revision surgeries. Here, we report preliminary data on clinical, laboratory and radiological outcomes in 19 patients who underwent surgical treatment and were followed for 6 months post-operatively.

The study was conducted at the Universitätsklinikum Münster in accordance with the Declaration of Helsinki. The protocol was approved by the local institutional review board (Ethics Committee of the Universitätsklinikum Münster). All patients gave written informed consent.

Patients and methods

UTN PROtect®

The UTN PROtect® implant is a titanium alloy (Ti-6Al-7Nb) nail used for intramedullary fixation of tibial shaft fractures. The device was CE-certified in August 2005. The fully resorbable antibiotic coating consists of an amorphous poly(γ, l-lactide) matrix containing gentamicin sulphate. The coating is applied through a proprietary process in which the entire surface of the nail is coated homogeneously [18]. The total amount of antibiotic contained on one implant ranges from around 10 to 50 mg, depending on the size of the implant. After implantation, the gentamicin sulphate is delivered to the surrounding tissue in a burst release profile starting at the moment of implantation. Based on studies of release kinetics of the UTN PROtect® implant (diameter 8 mm, length 330 mm) in deionised water, over 40% of the antibiotic is released within 1 h, 70% within 24 h and 80% within 48 h after implantation.

Study design

This investigation was a single-arm clinical study of UTN PROtect® for operative stabilization of diaphyseal fractures of the tibial shaft. All patients were enrolled and treated by different surgeons within one center, Universitätsklinikum Münster, Münster, Germany. The treating surgeon was free to use the implant in various indications. This study started with definite treatment of the fractured tibia using the...
antibiotic-coated intramedullary nail. The surgical procedure was performed in accordance with standard practices and with the manufacturer’s instructions for use of the UTN PROtect®. Follow-up visits were performed at 5 weeks, 3 and 6 months post-operatively.

Inclusion and exclusion criteria

Patients were included in the study if they met the following criteria: adult patients of age 18 years or more, having open or closed tibial shaft fractures amendable for intramedullary nailing, having failed previous therapies following tibial fractures and provided signed informed consent. Patients were excluded if they were pregnant, breast-feeding or planning to become pregnant during the study, or if they had consumptive or malignant primary disease, a life expectancy of < 3 months, a known allergy to aminoglycosides, or a condition that made it impossible to obtain informed consent (i.e. a physical or mental incapacity, a history of drug and alcohol abuse, were unlikely to cooperate, or were declared legally incompetent).

Antibiotic treatment

The surgeon was free to continue with the standard antibiotic regimen to treat fracture pattern, soft tissue damage and associated injuries. Reasons and duration for post-operative antibiotic therapy were documented throughout the follow-up period.

Data collection

The time from the accident to nail implantation was registered, as well as the patient’s history of previous procedures and infections. Patient data were recorded at the time of the accident and during the hospital stay. Data on infections and other adverse events were collected throughout the follow-up period. Laboratory parameters analysed were C-reactive protein, leukocyte count, haemoglobin and serum gentamicin.

SF-36 scores

The SF-36 physical and mental scores were measured at 6 months post-operatively. The scores are derived from the SF-36 measure of general health (quality of life) status. A SF-36 physical score of 50 ± 10 (mean ± standard deviation) is considered normal [21].

Radiographic assessments

Conventional radiographs of the fractured limb in two planes with the adjacent knee joint, as well as radiographs of the ankle were performed for all patients. As per protocol, radiographs were obtained at time intervals that reflected standard practice: before surgery, intra-operatively, and post-operatively at 5 weeks (±1 week), 3 months (±2 weeks) and 6 months (±2 weeks) after surgery. Patients were not exposed to additional radiation solely for study purposes.

Evidence of bone union was determined by radiographic assessment of four cortices per patient. Consolidated fracture healing was defined as the bridging of at least three of four cortices without weight bearing in the anterior-posterior (AP) and lateral view of the standard radiograph of the tibia, as previously described [11]. The radiographs were evaluated by three independent and blinded radiologists.

Results

Patient characteristics

A total of 21 patients (13 men; 8 women) underwent surgical treatment with UTN PROtect® from August 2005 to December 2007 (see Table 1). The mean age of the patients was 47.7 years (range 18–82 years). The mean body weight was 76.4 kg (range 40–120 kg) and mean height was 1.74 m (range 1.55–1.90 m). Three patients had a history of smoking and one patient had a history of diabetes.

Of the 21 patients, 19 completed 6 months of follow-up; one patient was lost to follow-up and another underwent amputation of the limb for reasons not related to infection. Nine patients had tibial fractures only and ten patients had multiple traumas with an injury severity score >16. On the basis of the AO classification, seven fractures were

| Table 1 Patient characteristics |
|-----------------------------|
| Characteristic              | Number |
| Age (years)                 |        |
| Mean                        | 47.7   |
| Min–max                     | 18–82  |
| Sex                         |        |
| Male                        | 13     |
| Female                      | 8      |
| Body weight (kg)            |        |
| Mean                        | 76.4   |
| Min–max                     | 40–120 |
| Height (m)                  |        |
| Mean                        | 1.74   |
| Min–max                     | 1.55–1.90 |
classified as closed fractures and 12 as open fractures. Of
the open fractures defined according to the classification
system of Gustilo and Anderson [8], three fractures were
I°, two were II° and seven were III° of which three were
grade IIIC. Based on the ASA classification, five patients
were rated as ASA I, 11 were rated as ASA II, two as ASA
III and one as ASA IV.

Treatment data

Five patients received immediate intramedullary nailing
within 24 h after sustaining the trauma. Due to additional
injuries, six patients received external fixation initially and
converted to intramedullary nailing within 4 weeks of the
injury. Eight patients received intramedullary nailing
between 4 weeks and 2 years after the initial fracture.
The mean operation time was 164.5 min (range
80–260 min). With respect to the characteristics of the
nails implanted, 4 nails were 8 mm in diameter, 13 nails
were 9 mm and 2 nails were 10 mm. The most frequently
used length was 345 mm (7 nails). During the operation,
the tibia was reamed in 16 patients.

All patients received perioperative antibiotic treatment
with cefuroxim. One patient received clindamycin due to a
history of allergy. Ten patients received antibiotic treat-
ment after surgery for an average of 9.4 days (range
3–30 days). Seven patients presented with severe soft tis-
sue injuries and required soft tissue stabilization with
additional surgery (e.g. vacuum therapy, skin grafting and
secondary skin closure).

Clinical outcomes

No deep wound infections were reported among the
19 patients after 6 months of follow-up. Three patients
reported adverse events, which required hospitalization and
therefore were classified as serious adverse events. One patient experienced a thromboembolic event and underwent
angioplasty. Another patient was hospitalized due to pain in
the left hip, which caused impairment of function and
mobility. The third patient suffered local wound healing
problems and required a second operation for debridement. Additionally, three patients required dynamization. All patients recovered from the events without complications.

SF-36 scores were measured for 15 patients at the
6-month follow-up visit. The mean SF-36 physical score
was 42.55 (range 19.35–56.68) and the mean SF-36 mental
score was 50.45 (range 27.48–64.98).

Laboratory parameters

Mean C-reactive protein levels remained below normal
range (<5 mg/L) throughout the study, irrespective of
whether patients had open or closed fractures. Patients with
open fractures (n = 12) had a higher mean C-reactive
protein level (4.8 mg/L) than patients with closed fractures
(3.0 mg/L) at 4–7 days post-operatively (Table 2). For all
patients, mean C-reactive protein levels peaked at 4.4 mg/L
at 4–7 days after surgery but thereafter returned to low
levels of <1.5 mg/L (Table 2). Leukocyte and haemoglo-
bin values did not differ markedly from baseline to
6 months after surgery (Table 2). Serum gentamicin levels
were <0.3 μg/ml in all patients at all follow-up assess-
ments after implantation of the UTN PROtect®
gentami-
cin-coated intramedullary nail.

Radiographic outcomes

Fracture healing was defined as the number of cortices that
had bridged as observed in radiographs obtained at
5 weeks, 3 months and 6 months after surgery. Fractures
were considered as healed when three or four cortices had
bridged or partially healed when one or two cortices had
bridged. The number of fully or partially healed fractures
increased steadily over time (Fig. 1). In total, the number
of bridged cortices were 26/76 at 5 weeks, 41/76 at
3 months and 53/76 at 6 months post-operatively.

At 5 weeks after surgery, most patients (89%) showed
partially healed fractures (11 patients with 1/4 and 6
patients with 2/4 bridged cortices). One patient had a
healed fracture (3/4) and one patient had no signs of
healing (0/4). At 3 months post-operatively, nine patients

| Table 2 Laboratory values at baseline and up to 6 months follow-up |
|---------------------------------------------------------------|
|                      | Baseline | Follow-up |
|                      | 4–7 Days | 5 Weeks  | 3 Months | 6 Months |
| **C-reactive protein (mg/L)**                                |          |          |          |          |
| All patients        |          |          |          |          |
| Mean                | 3.1      | 4.4      | 1.2      | 0.8      | 1.2      |
| Min–max             | 0.5–12.7 | 0.5–16.1 | 0.5–6.8  | 0.1–4.1  | 0.2–11.5 |
| Open fractures      |          |          |          |          |
| Mean                | 3.0      | 4.8      | 1.4      | 0.9      | 1.4      |
| Min–max             | 0.5–12.7 | 0.5–16.1 | 0.5–6.8  | 0.1–4.1  | 0.2–11.5 |
| Closed fractures    |          |          |          |          |
| Mean                | 3.7      | 3.0      | 0.9      | 0.6      | 0.5      |
| Min–max             | 0.7–8.5  | 1.7–4.8  | 0.5–2.0  | 0.5–0.8  | 0.5–0.6  |
| **Leukocyte count (×10⁹/L)**                                |          |          |          |          |
| Mean                | 9.8      | 7.8      | 7.1      | 7.1      | 6.4      |
| Min–max             | 4.9–18.6 | 2.8–14.1 | 3.6–10.4 | 0.5–10.4 | 3.4–8.9  |
| **Haemoglobin (g/dL)**                                     |          |          |          |          |
| Mean                | 12.6     | 11.8     | 13.0     | 14.0     | 14.0     |
| Min–max             | 9.1–16.4 | 7.3–16.4 | 9.5–15.7 | 10.1–16.5| 9.9–17.0 |
In this study, the use of UTN PROtect® gentamicin-coated intramedullary nail in the surgical treatment of open and closed fractures of the tibial shaft resulted in good clinical, laboratory and radiological outcomes within 6 months after surgery. The study population included patients with complex tibial fractures, severe soft tissue damage, or multiple traumas, as well as late revision cases. The use of UTN PROtect® did not affect or change the indicated surgical procedure. No deep wound infections were observed in our patients who showed greater complexity than those evaluated in previous studies of intramedullary tibial nailing [5, 9, 14]. One patient had superficial wound healing problems and was treated with surgical debridement. There were no additional implant-related adverse events. Two additional patients required dynamization. All patients recovered well from these events without complications. Fracture union progressed steadily over time post-operatively. At the follow-up visit at 6 months, 58% of patients showed healed fractures (three or four bridged cortices) while the remaining 42% showed partially healed fractures (one or two bridged cortices). There were no non-unions among the 19 patients who completed the 6 months of follow-up.

Infections are an infrequent but important complication of surgical treatment of long bone fractures, particularly in the tibia. Estimated rates of infection depend on the type and severity of fracture and the extent of soft tissue damage. Moreover, bone infections associated with mechanical devices such as implants are especially difficult to treat. In serious cases, the only effective treatment involves removal of the implant, multiple revisions with surgical debridement and intensive antibiotic therapy. Systemic antibiotics are accepted as standard prophylactic treatment. However, there are several limitations of systemically delivered antibiotics. Damage to vascularisation and impaired diffusion into the lumen due to reaming and intramedullary nailing may prevent systemic antibiotics from reaching the bone and surrounding tissue in concentrations high enough for an effective bactericidal action [17]. Other limitations include systemic toxicity and poor penetration into ischemic or necrotic tissues.

**Discussion**

In this study, the use of UTN PROtect® gentamicin-coated intramedullary nail in the surgical treatment of open and closed fractures of the tibial shaft resulted in good clinical, laboratory and radiological outcomes within 6 months after surgery.
In recent literature, a few studies are available, which give hints that solid nails are more resistant against infection compared with cannulated nails [10]. These studies are based only on animal experiences, but there exist no information about the differences of solid and cannulated nails in clinical use. Additionally, modern nailing systems are more or less completely cannulated systems. Occurrence of infection depends more on fracture morphology and soft tissue damage than to nail design.

The main goal of locally delivered antibiotics is to prevent bacterial colonization of the implant surface, thereby reducing the risk of implant-related infections. Another benefit of local delivery systems is that high concentrations of the antibiotic are achieved in the desired area without high systemic doses and associated side effects. In this study, very low serum gentamicin levels of less than 0.3 µg/ml were detected within 6 months after implantation of the UTN PROtect®.

PLA coatings, originally designed to enhance osseointegration of implants, have shown effectiveness as a matrix for controlled release of bioactive substances [12, 13, 18]. Gentamicin-loaded PLA coating of orthopaedic implants offers several advantages over other local delivery systems. Coated implants release the antibiotic directly at the implant surface, thereby avoiding the need for additional delivery devices such as coated collagen sponges. Moreover, PLA matrices are resorbable unlike PMMA beads and show a more sustained release of antibiotics compared with collagen sponges. Therefore, PLA coatings combine the advantages of the sustained release of PMMA beads and the biodegradability of collagen sponges. In our study, analysis of explanted nails indicated that gentamicin was completely resorbed within the 6-month follow-up period (data not shown). This minimizes the risk of generating resistant bacterial strains associated with long-term exposure to antibiotics. Nonetheless, there are no data from comparative studies on the effectiveness of different local prophylactic antibiotic systems, in particular those loaded with gentamicin.

In a pilot study of 8 patients with open tibial fractures who were treated with intramedullary nailing using the UTN PROtect®, no infections were observed after 1 year and all fractures consolidated within 6 months [17]. The present study provides further evidence of the lack of deep wound infections after intramedullary fixation of closed and open tibial fractures with the UTN PROtect® gentamicin-coated tibia nail. Consistent with the reduction in the risk of infection, local delivery of gentamicin was associated with good control of inflammation during the initial phase after surgery. Although C-reactive protein, an inflammatory marker, showed a slight peak within 7 days after surgery, mean levels remained within normal range (<5 mg/L) throughout the study and decreased to low levels after 6 months for all patients. In addition, leukocyte counts and haemoglobin levels remained constant during the study period.

Bone infections negatively affect fracture healing, limb function and quality of life. In the present study, there were no deep wound infections and only one superficial wound healing problem among 19 patients within 6 months. This low rate of infection was associated with good fracture healing over time. The percentage of bridged cortices increased from 34% (26/76) at 5 weeks to 70% (53/76) at 6 months after surgery. At the final follow-up visit, all patients showed fully or partially healed fractures. Full weight-bearing capacity was achieved in 13 patients (68%) and partial weight bearing in 6 patients after 6 months. The mean SF-36 physical score at 6 months after surgery in patients who recovered from tibia fracture is 39.1 [1]. This is slightly less than the outcome in this study (42.6). However, the patient number is too small for statistical analysis; it is just possible to show tendencies. Due to the small number of patients the authors of this study do not dare to conclude that antibiotic-coated IM nails prevent osteomyelitis in severe tibia fractures; nevertheless, no serious adverse events were seen in this study group. Local administration of continuously released antibiotics at the fracture site may be an additional tool to manage difficulties to treat tibia fractures.

Conclusion

Implant-related infections pose an important challenge in the surgical treatment of tibial shaft fractures. Local administration of antibiotics, such as through antibiotic coating of implants, might minimize the risk of infections and improve clinical and radiological outcomes. In this prospective, non-randomized case series, we showed that use of UTN PROtect® gentamicin-coated intramedullary nail to treat closed and open tibial fractures was associated with an absence of deep wound infections, good fracture healing and increasing weight-bearing capacity after 6 months. These good outcomes were observed even in our series of patients with complex tibial fractures and multiple traumas. Given these promising data, further studies are warranted to establish the use of UTN PROtect® gentamicin-coated devices for the prevention of post-surgical infection in trauma patients and in revision cases.

Conflict of interest The authors disclose no conflict of interest. The authors received research grants or other funding from the AO-Foundation. No Author served as consultant to and received any honoraria.
References

1. Busse JW, Bhandari M, Guyatt GH et al (2009) Use of both short musculoskeletal function assessment questionnaire and short form-36 among tibial-fracture patients was redundant. J Clin Epidemiol 62(11):1210–1217. doi:10.1016/j.jclinepi.2009.01.014

2. Court-Brown CM, McBirnie J (1995) The epidemiology of tibial fractures. J Bone Joint Surg Br 77(3):417–421

3. Diefenbeck M, Muckley T, Hofmann GO (2006) Prophylaxis and treatment of implant-related infections by local application of antibiotics. Injury 37(Suppl 2):S95–S104. doi:10.1016/j.injury.2006.04.015

4. Fuchs T, Schmidmaier G, Raschke MJ et al (2008) Bioactive-coated implants in trauma surgery. Eur J Trauma Emerg S 34(1):60–68. doi:10.1007/S00068-006-6110-5

5. Gaebler C, Berger U, Schandelmaier P et al (2001) Rates and odds ratios for complications in closed and open tibial fractures treated with unreamed, small diameter tibial nails: a multicenter analysis of 467 cases. J Orthop Trauma 15(6):415–423

6. Gosselin RA, Roberts I, Gillespie WJ (2004) Antibiotics for preventing infection in open limb fractures. Cochrane Database Syst Rev (1):CD003764. doi:10.1002/14651858.CD003764.pub2

7. Govender S, Csimma C, Genant HK et al (2002) Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am 84-A(12):2123–2134

8. Gustilo RB, Anderson JT (2002) JSBS classics. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. Retrospective and prospective analyses. J Bone Joint Surg Am 84-A(4):682

9. Hettfleisch J, Schottle H (1993) Local preventive antibiotic treatment in intramedullary nailing with gentamycin impregnated biomaterials. Aktuelle Traumatol 23(2):68–71

10. Horn J, Schlegel U, Krettek C et al (2005) Infection resistance of unreamed solid, hollow slotted and cannulated intramedullary nails: an in vivo experimental comparison. J Orthop Res 23(4):810–815. doi:10.1016/j Orrthres.2004.11.006

11. Johnson EE, Urist MR, Finerman GA (1988) Repair of segmental defects of the tibia with cancellous bone grafts augmented with human bone morphogenetic protein. A preliminary report. Clin Orthop Relat Res (236):249–257

12. Lucke M, Schmidmaier G, Sadoni S et al (2003) Gentamicin coating of metallic implants reduces implant-related osteomyelitis in rats. Bone 32(5):521–531 S8756328203000504[pii]

13. Lucke M, Schmidmaier G, Sadoni S et al (2003) A new model of implant-related osteomyelitis in rats. J Biomed Mater Res B Appl Biomater 67(1):593–602. doi:10.1002/jbtm.10051

14. Maurer DJ, Merkow RL, Gustilo RB (1989) Infection after intramedullary nailing of severe open tibial fractures initially treated with external fixation. J Bone Joint Surg Am 71(6):835–838

15. Noumi T, Yokoyama K, Ohtsuka H et al (2005) Intramedullary nailing for open fractures of the femoral shaft: evaluation of contributing factors on deep infection and nonunion using multivariate analysis. Injury 36(9):1085–1093. doi:10.1016/j.injury.2004.09.012

16. Petrisor B, Anderson S, Court-Brown CM (2005) Infection after reamed intramedullary nailing of the tibia: a case series review. J Orthop Trauma 19(7):437–441. doi:00005131-200508000-00001

17. Schmidmaier G, Lucke M, Wildemann B et al (2006) Prophylaxis and treatment of implant-related infections by antibiotic-coated implants: a review. Injury 37(Suppl 2):S105–S112. doi:10.1016/j.injury.2006.04.016

18. Schmidmaier G, Wildemann B, Stemberger A et al (2001) Biodegradable poly(D, L-lactide) coating of implants for continuous release of growth factors. J Biomed Mater Res 58(4):449–455

19. Stengel D, Bauwens K, Sehouli J et al (2001) Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis 1(3):175–188. doi:10.1016/S1473-3099(01)00094-9

20. Tsukayama DT (1999) Pathophysiology of posttraumatic osteomyelitis. Clin Orthop Relat Res (360):22–29

21. Ware JE Jr (2000) SF-36 health survey update. Spine (Phila Pa 1976) 25(24):3130–3139

22. Young EJ, Sugarman B (1988) Infections in prosthetic devices. Surg Clin North Am 68(1):167–180