

Expert Tibial Nail PROtect



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Value Analysis Brief

EXECUTIVE SUMMARY

Surgical site infection (SSI) remains a feared complication in orthopaedic and trauma surgery due to its potentially devastating consequences. In patients with tibial shaft fractures infection may lead to prolonged treatment, compromised clinical outcomes and in some cases even limb amputation.¹⁻⁴ Despite advances in prophylactic care, the risk of an infection remains relatively high for certain patients. There are numerous risk factors for the development of an infection following fixation surgery, which are both patient and procedure related, such as: obesity, diabetes, smoking, immunosuppression, open fracture, severity of injury, presence of an implant or fixation device, existence of multiple injuries at various sites of the body (polytrauma).⁴⁻⁷

Ongoing research is aimed at identifying new prevention options such as novel antibiotic delivery systems, other antibacterial agents and modification of orthopaedic implants.⁸⁻¹⁰ Implant coatings have gained attention due to their potential to address implant-related infections.⁸⁻¹⁰ One of the promising prevention options identified by clinical experience is the PROtect Coating featured in Expert Tibial Nail PROtect, an antibiotic coated intramedullary nail.^{9,11,12}

This value analysis brief introduces the epidemiology and treatment pathway of tibial shaft fractures and provides extensive information on the following aspects of infection:

- Epidemiology, risk factors and development mechanism
- Consequences of an infection for the patient, healthcare providers and the health service overall
- Unmet clinical need based on existing prophylactic regimens
- Value of local antibiotic delivery systems and specifically ETN PROtect, when added to systemic antibiotic prophylaxis

Throughout the document there is a particular focus on data specific to open tibial shaft fractures, as these are widely considered as more challenging to treat and have been clearly associated with an increased risk of infection compared to closed fractures.^{6,13} An overview of the structure and key information presented under each section is displayed below.

ETN PROtect Value Analysis Brief

TIBIAL SHAFT FRACTURES	EPIDEMIOLOGY	Approximately 23.5% of tibial fractures are open fractures and of those 57.3% are grade III fractures in the Gustilo-Anderson classification (GAIll), presenting with severe soft tissue damage.
	TREATMENT	Open tibial shaft fractures are considered as more challenging to treat and are often associated with a high incidence of complications such as non-union, compartment syndrome and infections.
INFECTION	EPIDEMIOLOGY	The rate of deep infection across all open tibia fractures treated with intramedullary nailing is 8.8%, increasing with severity of soft tissue injury up to 14.4% for GAIll fractures.
	RISK FACTORS	An open fracture injury and the presence of an implant are among the key patient and procedure related risk factors for the development of an infection.
	BIOFILM	The presence of an implant increases the risk of an infection because of bacteria colonizing the implant surface and forming a biofilm. Eradication of the bacterial biofilm requires up to 1000 times higher antibiotic concentrations than those required for “free-floating” bacteria.
	CLINICAL BURDEN	Patients with an infection following a tibia fracture may have to go through a long and complex treatment pathway, which might lead to an amputation.
	ECONOMIC BURDEN	Treatment costs for patients with an infection following a tibia fracture were shown to be up to 3.5 times higher compared to those for patients with no infection.
	INFECTION PREVENTION	Adding locally administered antibiotics to systemic antibiotic prophylaxis was shown to reduce the infection rate for GAIll patients from 14.4% to 2.4% and for GAIllB&C patients from over 31% to 9%.
	ETN PROtect	ENHANCED PATIENT SAFETY
TARGETED PROTECTION		Developed to deliver targeted protection against localized infection.
CLINICALLY PROVEN		Clinical experience with supporting evidence.

TIBIAL SHAFT FRACTURES

Epidemiology

Approximately 23.5% of tibial fractures are open fractures and of those 57.3% are grade III fractures in the Gustilo-Anderson classification (GAIII), presenting with severe soft tissue damage.^{14,15}

Fractures of the tibial diaphysis account for 44.7% of long bone fractures and 1.9% of all fractures.^{16,17} The most common causes of tibial fracture are walking, indoor activities and sports.¹⁸ A study investigating the epidemiology of tibial shaft fracture gave an annual incidence of 16.9 fractures per 100,000 people. Males are more likely to suffer from this type of fracture, with an increased prevalence of 21.5/100,000/year vs 12.3/100,000/year in females. Furthermore, the average age that males sustain a tibial fracture is between 10-20 years, whilst women are most frequently affected between 30-40 years.¹⁸

Tibial fractures can be either open or closed. According to an epidemiological study 23.5% of patients that

sustain a tibial fracture present with an open injury.¹⁴ The increased proportion of open tibial fracture compared to other long bone fracture is due to the limited soft tissue coverage of the tibia.^{15,19} The amount of time that the fracture takes to heal depends on the severity of the injury. Low energy fractures can heal within 16 weeks, however more severe fractures with significant amounts of soft tissue loss may require treatment for up to a year.²⁰

There are several classification systems used to describe the severity of a tibial fracture, including the AO classification, which defines fractures based on fracture location (bone segment) or fracture site morphology.²¹ The Oestern and Tschene classification system can be used to classify open and closed fractures by soft tissue injury.²² The most commonly used classification system for open fractures is the Gustilo-Anderson system, which grades the fracture according to severity of soft tissue damage (as shown in Table 1).

Gustilo-Anderson classification	Extent of damage
Type I	Wound size <1cm with minimal soft tissue damage
Type II	Wound size >1cm with minimal soft tissue damage
Type IIIa	Wound size >1cm with extensive soft tissue damage with adequate coverage
Type IIIb	Wound size >1cm with extensive soft tissue coverage with inadequate coverage
Type IIIc	Wound size >1cm with extensive soft tissue damage with inadequate coverage and extensive arterial and vascular damage

Table 1: Gustilo-Anderson classification of open fractures, adapted from Bode et al. 2012²²

The majority of open fractures are grade III fractures in the Gustilo-Anderson classification¹⁵, which are more complex fractures, presenting with extensive soft tissue damage and possibly inadequate coverage

and extensive arterial and vascular damage. The epidemiology of open tibial fractures is presented in Figure 1.

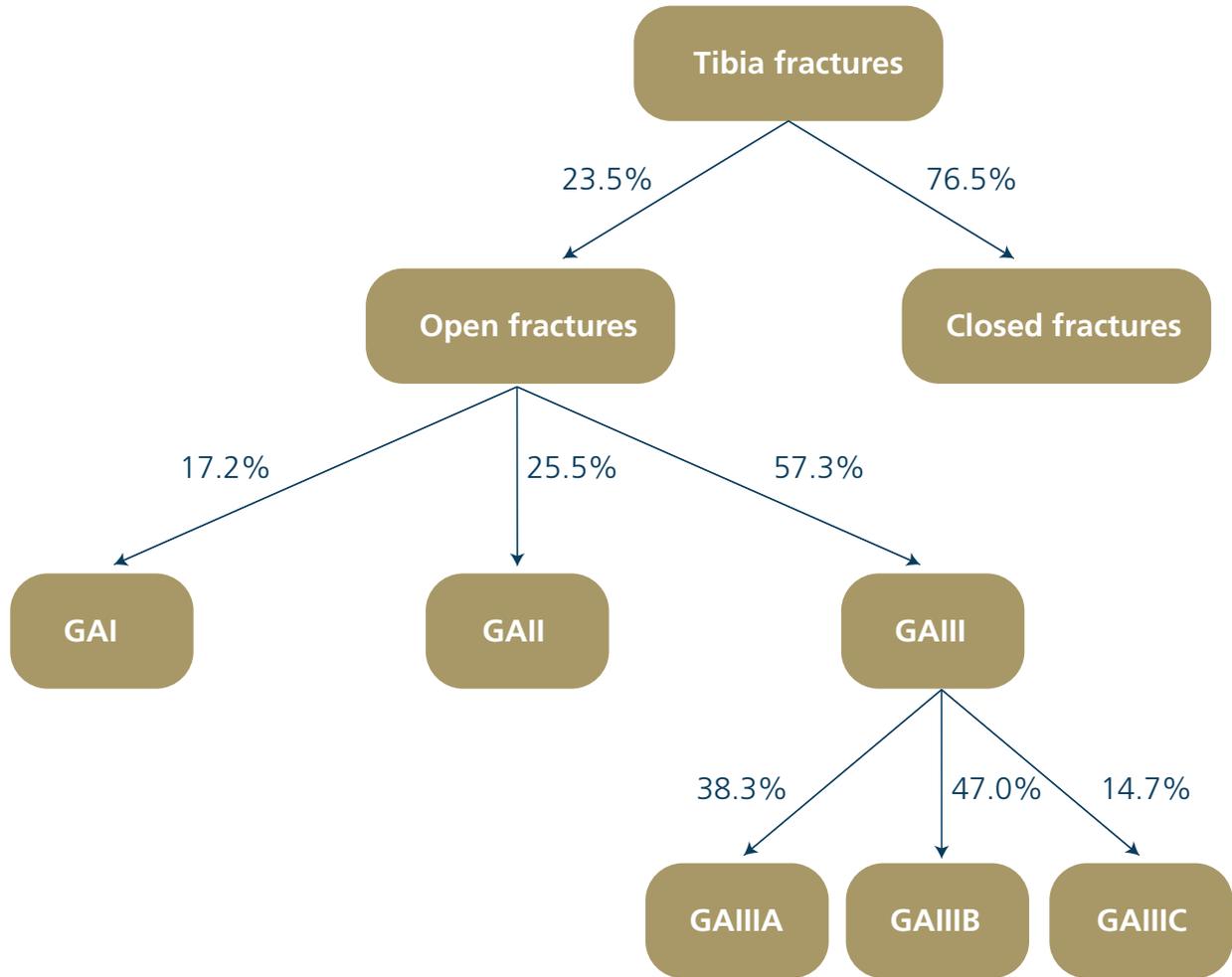


Figure 1: Epidemiology of open fractures according to Gustilo-Anderson classification^{14,15}

TIBIAL SHAFT FRACTURES

Treatment

Open tibial shaft fractures are considered as more challenging to treat and are often associated with a high incidence of complications such as non-union and infections.^{13,15}

The fracture pattern and parameters such as achieving solid bony union, avoiding infection, regaining full function of the injured limb and the time required to be able to weight bear fully^{22,23} will influence the selection of medical treatment.²²⁻²⁴ The primary goal of treatment for tibial shaft fractures is to reduce the displaced bone fragments (reposition of fractured bone or anatomical restoration) and to restore normal function of the leg.²⁵ The treatment choice should allow the patient to be restored with the best possible function with minimum risk of complication.^{20,25} In general, displaced or unstable fractures are treated surgically to reduce the risk of mal-union or non-union.¹⁹ Surgical treatments are also commonly applied to high energy trauma, polytrauma, segmental fracture and all open injuries. In terms of surgical treatments, the options are: external fixation – an external metal frame connected to internal stabilizing pins, percutaneous or compression plates, and intramedullary nailing – the insertion of a titanium nail into the intramedullary canal of the tibia.^{26,27}

Open tibial shaft fractures are considered more challenging to treat as the bone must be reduced in conjunction with managing the flesh wound.¹³ In terms of surgical fixation intramedullary nailing appears to have become the preferred technique^{27,28} with a number

of advantages compared to plating highlighted in the literature, such as avoidance of further disruption of the soft tissues and periosteum, the potential to allow for immediate postoperative weight bearing²⁶ and lower deep wound infection rates.⁵ The use of external fixation has decreased, however it is still used in the treatment of multiple trauma and severely contaminated fractures, and can be used before a second-stage internal fixation procedure is used.^{22,26}

Open tibial shaft fractures are often associated with a high incidence of complications, due to the precarious blood supply to the tibia, the high risk of infection and the necessity of rapid surgical intervention. Complications include non-union, compartment syndrome, infection and amputation.¹⁵ A study reported the mean number of operations until union was achieved at 4.29 (1-23) operations per patient, reaching 10.8 operations per patient for the more severe fractures graded Gustilo-Anderson IIIC.²⁹ According to a systematic review compartment syndrome affects up to 10% of patients with open fractures up to grade IIIB in the Gustilo-Anderson classification and approximately 85.7% of patients with a grade IIIC fracture.¹⁵ Non-union was shown to affect 23% of patients presenting with an open fracture.³⁰ According to the Swedish National Patient Register (1998–2010, n=3777 patients) approximately 3.6% of open tibial fractures result in amputation, and older patients are at a higher risk of amputation compared with younger patients.³¹

INFECTION

Epidemiology

The rate of deep infection across all open tibia fractures treated with intramedullary nailing is 8.8%, increasing with severity of soft tissue injury up to 14.4% for GIII fractures.⁵

Infection following fracture fixation is a serious complication with potentially devastating consequences for the patient. It results in prolonged treatment and compromised outcomes.^{1,2,4} It is associated with impaired fracture healing (delayed union or non-union or mal-union) and in some cases might result in limb amputation.^{2-4,32}

Surgical site infections can be classified into soft tissue infections (superficial or deep wound) and bone infections i.e. osteomyelitis.^{33,34} A bone infection can develop by direct contamination (e.g. open fractures) or from a contiguous site or implant or by spreading via the blood stream (hematogenously).³⁵ The term “deep infection” is often used in the literature to refer to infections involving deeper tissues such as muscular fascia and bone.⁶

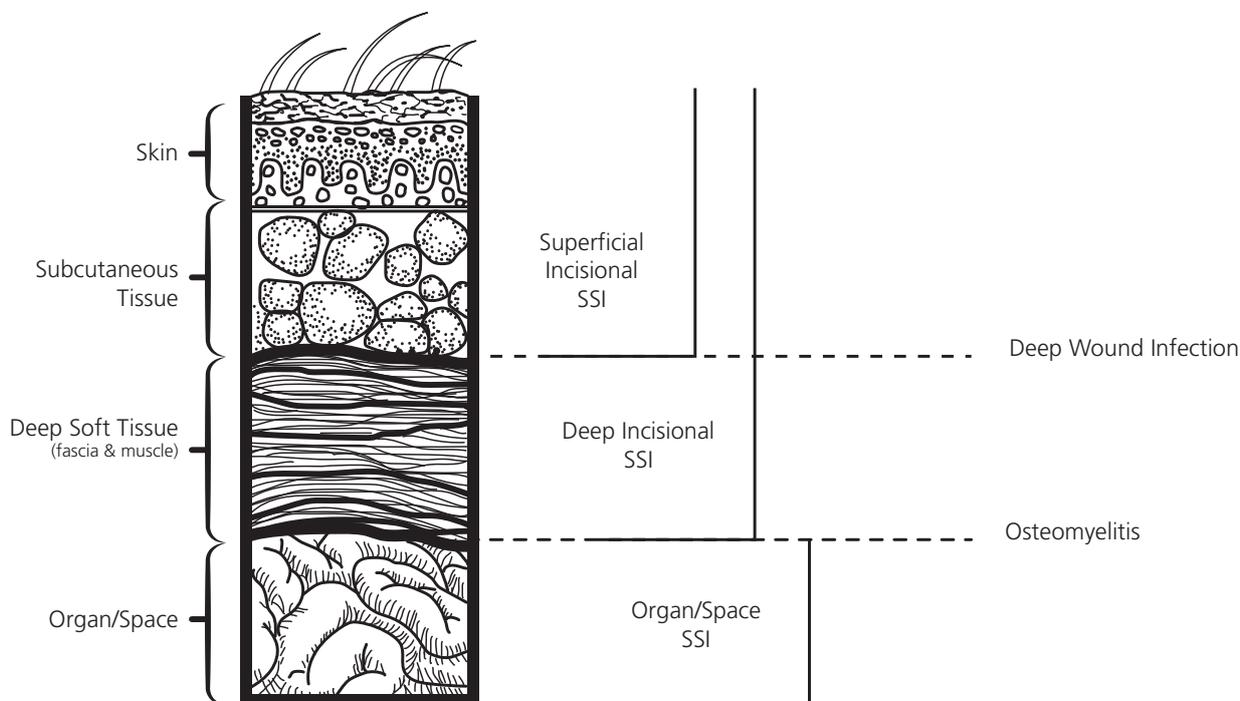


Figure 2: Types of surgical site infection (SSI) according to the type of tissue involved (Adapted from Mangram 1999)³⁶

Other classifications are based on the time between surgery and clinical manifestation.^{1,37,38} “Early” infections, occurring in the immediate postoperative period (within 2-6 weeks) are usually infections of the soft tissue.³⁷ A delayed infection manifesting 2-9 months postoperatively is assumed to be present in the bone and is associated with delayed wound healing and possibly with an impaired fracture healing response.³⁷ “Late” infection (>9 months post-operatively) represents a

chronic osteomyelitis,³⁷ characterised by the presence of a sequestrum, a necrotic piece of devascularised bone.⁴ Clinical symptoms will vary in magnitude and usually will include pain at the involved site, erythema, swelling and a draining sinus, without fever.⁴ The majority of cases will also have a recorded history of an atrophic non-union following an open fracture or internal fixation of a closed fracture.⁴

Reported infection rates following tibial fractures vary depending on the definition of infection used, the type and severity of the fractures. In a systematic review and meta-analysis by Craig et al. 2014 looking into deep wound infection rates in open tibia fractures treated with intramedullary nailing, the infection rate across all open tibia fractures was 8.8%.⁵ It increased with severity of soft tissue injury as follows: 1.7% for GAI,

3.1% for GAI and for GAI 14.4%.⁵ For the more severe GAI fractures, the review identified an infection rate of 2.4% for GAI A and over 31% for GAI B&C.⁵ Similar results were found in an earlier systematic review and meta-analysis by Papakostidis et al. 2011 with regard to deep infection rates in open tibia fractures treated with intramedullary nailing.^{15, 39-42}

Publication	Infection definition	Study type	Type I	Type II	Type III Fracture		
					IIIa	IIIb	IIIc
Khatod et al., 2003 ³⁹	Osteomyelitis	Retrospective cohort study	4.3%	2.2%	0%	16.7%	25%
Singh et al., 2012 ⁴⁰	Osteomyelitis	Retrospective cohort study	-	-	0%	20.5%	0%
Matos et al., 2015 ⁴¹	Deep infection	Retrospective cohort study	3.2 %	22.6 %	22.6 %	41.9 %	9.7%
Chua et al., 2012 ²⁹	Deep infection	Retrospective cohort study	8.5%	9.4%	21.1%	44.6%	
Saddawi-Konefka et al., 2008 ⁴²	Osteomyelitis	SR*	-	-	-	17.9%	
Papakostidis et al., 2011 ¹⁵	Deep infection	SR*	1.7%	3.1%	2.4%	9.2%	-
Craig et al., 2014 ⁵	Deep wound infection	SR*	1.7%	3.1%	2.4%	31%	

*SR= systematic review and meta-analysis

Table 2: Infection rates following tibial fractures depending on infection classification, fracture pattern and severity

INFECTION

Risk factors

An open fracture injury and the presence of an implant are among the key patient and procedure related risk factors for the development of an infection.^{6,7}

Risk factors for the development of a surgical site infection may be classified into patient-related and

operation-related factors.⁷ Among trauma patients, several factors have been reported to influence the risk of an infection such as high Injury Severity Scores (ISS), morbid obesity, older age, male gender, type of trauma (blunt or penetrating), wound classification, use of prophylactic antibiotics, multiple transfusions, and multiple surgical procedures to treat the fracture.^{41,43}

Risk factors for the development of a surgical site infection (SSI) following an orthopedic procedure* (adapted from ter Boo 2015)	
Patient factors	Operative factors
Extremes of age Poor nutritional state Obesity (>20% of ideal body weight) Diabetes mellitus Smoking Infections at sites other than the surgical site Inflammatory arthritis Malignancy Bacterial colonization (e.g. nares colonization) Immunosuppression (steroids, other immunosuppressive drug use, cytotoxic drugs or previous antibiotics) Preoperative hospitalization Prolonged postoperative hospital stay (nosocomial infection)	Too short surgical scrub (shorter than 2 min) Poor skin antisepsis Preoperative shaving Type of agent used for preoperative skin preparation Emergency procedure Length of operation Antimicrobial prophylaxis Operating theater ventilation Inadequate instrument sterilization Traumatic or unfamiliar surgical technique (hematoma, devitalized tissue, dead space, electro cautery etc.) Foreign material in surgical site (orthopedic implant, fracture fixation devices) Surgical drains Surgical technique (hemostasis, poor closure, tissue trauma) Postoperative hypothermia

* Factors are not ranked according to effect on risk of infection or any other criterion

Table 3: Risk factors for the development of a surgical site infection (SSI) following an orthopedic procedure (adapted from ter Boo 2015)⁷

Similarly risk factors that have been associated with an increased risk of developing a deep infection in patients with a tibia fracture treated with intramedullary nailing include obesity/Body Mass Index (BMI), diabetes,

smoking, open fractures, Gustilo-Anderson grade, contamination, trauma mechanism, polytrauma and primary external infection.⁴⁻⁶

INFECTION

Biofilm formation

The presence of an implant increases the risk of an infection because of bacteria colonizing the implant surface and forming a biofilm.^{7,8,35,38} Eradication of the bacterial biofilm requires up to 1000 times higher antibiotic concentrations than those required for “free-floating” bacteria.^{8,44}

Infections following an orthopaedic trauma procedure have often been associated with the presence of an implant.^{7,8,35,38} Implanted devices are highly susceptible to bacterial infection³⁸ and have been highlighted in the literature as a key risk factor for the development of an infection.⁷ The most common pathogens associated with implant related infections are *Staphylococcus epidermidis* and *Staphylococcus aureus*.⁴⁵ Other commonly identified pathogens are presented in Table 4.

Pathogen Frequency	(%)
<i>Staphylococcus aureus</i>	30
Coagulase-negative staphylococci	22
Gram-negative bacilli	10
Anaerobes	5
Enterococci	3
Streptococci	1
Polymicrobial	27
Unknown	2

Table 4: Commonly identified pathogens causing infections associated with fracture-fixation devices (adapted from Trampuz et al. 2006).⁴⁶

From the moment an intramedullary nail is inserted a ‘race to the surface’ ensues, where host immune cells compete with bacteria to colonize on the surface of the implant.⁴⁷ Bacterial adhesion to the surface of the implant is greatly affected by the material composition of the implant. If the bacteria successfully adhere to the implant surface a permanent attachment develops, and micro-colonies of bacteria begin to form (biofilm).^{8,9,35,48}

The process from bacterial adhesion to the production of a mature biofilm is normally completed within 12 to 18 h.¹⁰ The bacteria can passively remain on the implant, and given the opportunity, for example due to reduced host immunity or poor tissue ingrowth, will overgrow and cause a clinical infection.⁴⁸

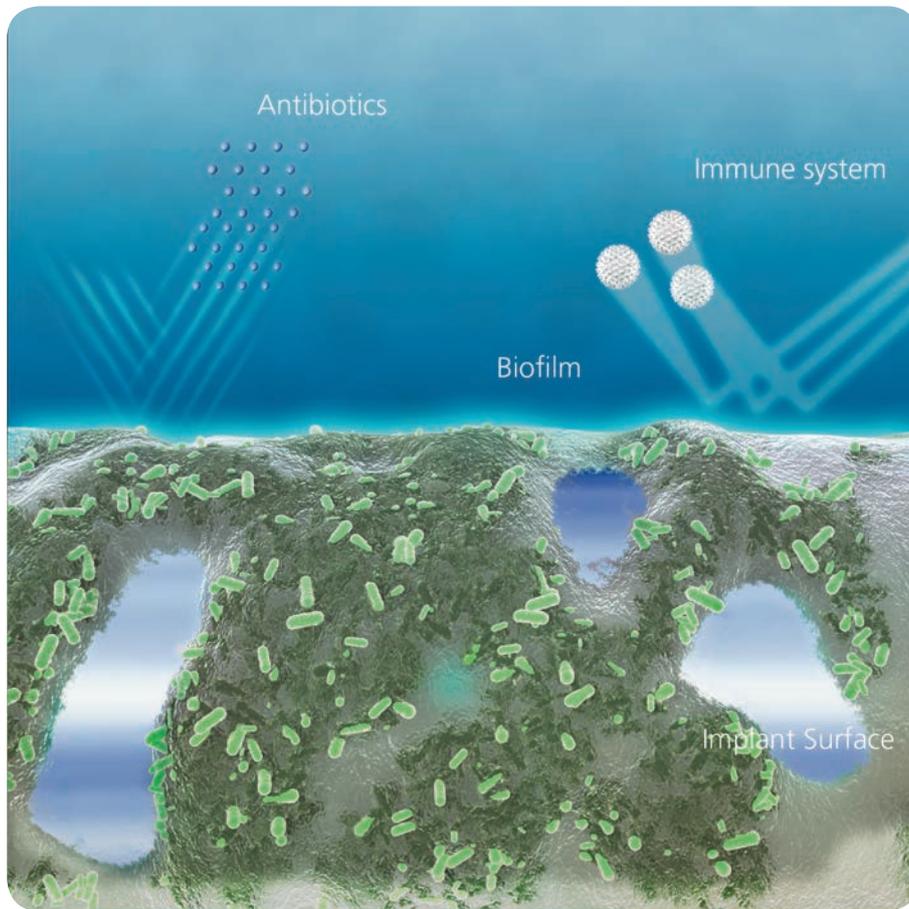


Figure 3: Biofilm formation

Bacterial biofilms are particularly difficult to treat as they are highly resistant/tolerant to antibiotics and other anti-microbial agents, as well as to host immune responses.^{7-9,35,48,49} Their eradication requires antibiotic concentrations that are 10–1000 times higher than that required for planktonic (free-floating) bacteria.^{8,44}

Such concentrations may lead to significant side effects, therefore it is important to combat the bacteria before a biofilm is established.^{44,8} Biofilm prevention is particularly important in open fractures where so many bacteria are present.

Clinical burden

Patients with an infection following a tibia fracture may have to go through a long and complex treatment pathway, which might lead to an amputation.^{3,4,35,37}

The main goals of infection treatment are fracture consolidation and prevention of chronic osteomyelitis.³⁸ The stage of the infection and the extent of fracture healing will define the treatment strategy.^{3,4,37} Timely and accurate diagnosis will be critical for the success of the treatment. The need for a thorough clinical evaluation and detailed diagnostic testing including a full blood cell count, C-reactive protein and erythrocyte sedimentation rate, radiographic imaging (to define the extent of bone involvement) and the culture of the infected tissue to identify the species of the bacteria and confirm antibiotic susceptibility.^{2,3,7,8,37}

While early soft tissue infections are usually treated with high doses of intravenous antibiotics, deep infections – i.e. infections involving deeper tissues such as muscular fascia and bone⁶ - will require surgical treatment for the debridement of the infected soft and bone tissue and appropriate wound closure, in addition to antibiotic administration.^{1,2,37} The removal of the nail followed by fixation revision may be required.³⁷ However, the implant may be left in place if it still provides stable fixation until the fracture has

Economic burden

Treatment costs for patients with an infection following a tibia fracture were shown to be up to 3.5 times higher compared to those for patients with no infection.⁵¹

Several studies have shown that infection following orthopaedic procedures can significantly increase the economic burden for healthcare providers due to increased length of hospital stay, readmissions, prolonged pharmacological treatment and reoperations.⁵²⁻⁵⁷ Data from long bone fracture reduction, hip replacement or hemiarthroplasty or screw fixation for proximal femoral fractures and knee arthroplasty, consistently reported 2-3 times higher treatment costs for patients that developed an infection compared to those that did not.⁵²⁻⁵⁷ Similarly, a study by Chern et al. showed that infection was the primary reason for readmission within 60 days

healed.^{1,3,37} It has been reported in the literature that of all removed intramedullary nails 7.1% are removed due to infection.⁵⁰

In cases of chronic osteomyelitis, treatment will be more complex and will require a multidisciplinary approach.^{3,4} Surgical management will often include appropriate debridement of the necrotic and infected tissues, removal of the implant, irrigation of the intramedullary canal and fracture stabilization in case of non-union, dead space and wound management and local antibiotic therapy in addition to systemic antibiotics.^{4,35,37} After an aseptic environment has been achieved the patient may have to undergo additional bone restoration treatment with bone grafts to address non-union or large bone defects due to debridement.^{4,37}

However, despite intensive treatment, therapeutic failures and recurrences are common with reported rates of 20 to 30%.⁴ For some patients e.g. the diabetic population, treatment failure might lead to amputation with devastating consequences for the patient.⁴ According to data from the Swedish National Patient Register (1998–2010, n=3777 patients), 16% of amputations following open tibia fracture treatment was attributed to chronic osteomyelitis.³¹

of fracture, for 50% of closed fracture patients and 91.7% of open tibia fracture patients.⁵⁸ In the European setting there is limited data available with respect to the actual cost of treatment. In a Danish study by Olesen et al. on patients with open tibia fractures treated with a free flap, the presence of infection increased the mean length of hospital stay from 28 to 63.8 days and the mean treatment costs from €49,301 to €67,958 for uninfected compared to infected fractures (p-values not reported).⁵⁹ Kendall et al. in the UK reported the mean length of hospital stay and treatment costs of patients with tibial osteomyelitis. For patients treated with limb salvage procedures alone length of stay was 15 days (10-27) and corresponding treatment costs were €16,718, while for patients whose treatment ended up in amputation length of stay was 13 days (8-17) and treatment costs were and €18,441.⁶⁰ Early results from a resource utilization and costing study aimed at estimating the clinical and economic burden associated with the treatment of infection in

patients with tibia fractures following intramedullary nailing, showed up to 3.5 times higher treatment costs for patients with a bone infection compared to those with no infection for the German healthcare setting. For patients with Gustilo-Anderson grade II fractures the mean incremental treatment cost for infected patients versus non-infected was €20,438, whereas for patients with Gustilo-Anderson grade III fractures

this was €27'401.⁵¹ These incremental treatment costs were attributed to i) the additional surgical procedures required to manage the infection e.g. debridement, irrigation, flap reconstruction, implant removal, bone grafting, amputation and ii) the prolonged hospital stay and readmissions in the general orthopaedic ward and the intensive care unit for patients with an infection.

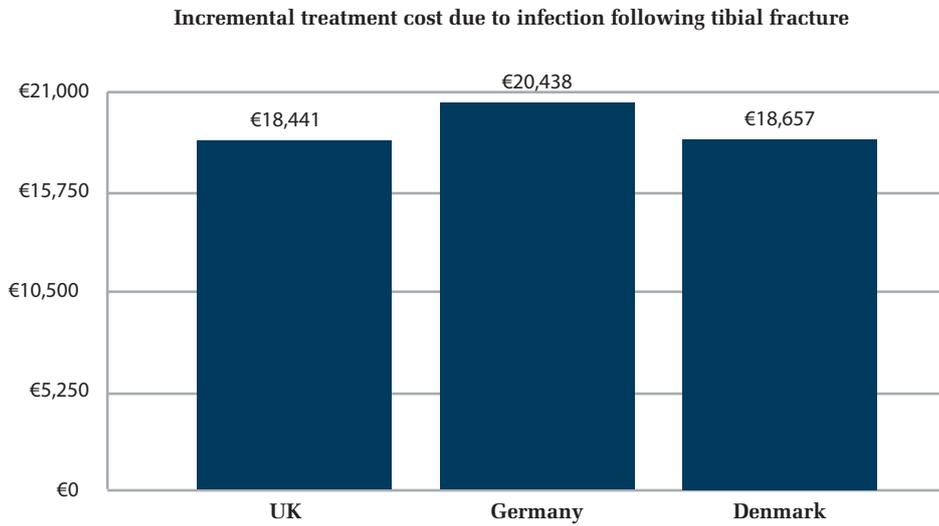


Figure 4: Incremental treatment costs attributed to the development of an infection following surgery for the fixation of a tibial fracture^{51,59,60}

Infection prevention

Adding locally administered antibiotics to systemic antibiotic prophylaxis was shown to reduce the infection rate for GAIII patients from 14.4% to 2.4% and for GAIIB&C patients from over 31% to 9%.⁵

Numerous patient-related and procedure related factors influence the risk of surgical site infection in surgical patients. Prevention requires a systematic approach addressing multiple risk factors, in order to reduce the risk of bacterial contamination and improve the patient's defenses. Good patient preparation, aseptic practice, attention to surgical technique, and antimicrobial prophylaxis are all essential for the prevention of surgical site infection.⁴³ To reduce the risk of infection, there is general consensus that wound cleaning and debridement should be performed within 6 hours of injury to remove potential contaminants.⁶¹ It has also been reported that early wound closure decreases the incidence of infection.⁶²

In open injury, antibiotics should be administered as prophylaxis to prevent colonisation of bacteria that may have survived debridement.²⁶ Antibiotics can be administered systemically e.g. intravenously and through local delivery systems.^{7,9,26} Guidelines advise prophylactic systemic administration of cephalosporin antibiotics, or in the case of severe fractures, cephalosporin in combination with aminoglycoside antibiotics.²⁶

Although systemic administration of antibiotics as prophylaxis is common practice worldwide, it has been associated with several limitations, such as the fact that efficacy is dependent on the correct timing of administration.¹⁰ In particular the ability of systemic antibiotics to reach the tissue-implant surface in high enough concentrations to eradicate bacteria and prevent the formation of a biofilm has been questioned.^{9,10}

The addition of local antibiotic delivery systems in prophylactic treatment is considered as a potential solution to these challenges and a means of further reducing the risk of infection.^{5,8,9} The local delivery of antibiotics is quite common in traumatology and joint replacement surgery. Poly(methyl methacrylate) (PMMA) cements have been broadly used as the carrier material of antibiotics, especially in joint replacement surgery. They have been shown to be effective prophylaxis for septic complications and to prevent bacterial colonization of newly implanted devices.^{7,9,63,64} Other

non-cement based systems include resorbable hydrogels containing antibiotics, which are used to coat the entire implant prior to implantation.⁶⁵ In traumatology the local antibiotic delivery systems used to prevent or treat bone and soft tissue infections come in the form of antibiotic loaded cement blocks, antibiotic loaded cement beads, intramedullary nails coated with antibiotic loaded cement, collagen fleeces loaded with antibiotics and more recently antibiotic coated nails.^{7-9,63}

The antibiotics most commonly used to deliver high local concentrations in cases of open fractures and osteomyelitis are Aminoglycosides – such as tobramycin and gentamicin- and vancomycin.⁶³ Gentamicin has a proven record of success as the most commonly used antibiotic for local application in combination with bone cement for prosthetics.⁶⁶ It has a concentration-dependent bactericidal activity and is effective against the bacteria most commonly responsible for deep wound infection: *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas*.⁶⁷ It has a low allergenic potential and shows a synergistic effect in combination with Cephalosporins.⁶⁷

Guidelines suggest the use of local antibiotic therapy in patients that have segmental bone loss, gross contamination or an established infection.²⁴ Locally applied antibiotics are advantageous as they deliver high concentrations of antibiotic to the implant site whilst systemic concentrations of antibiotic remain low, which reduces the risk of systemic toxicity. Furthermore, there is a high and sustained delivery of antibiotic to the desired location, where physiology may hinder the efficacy of systemic antibiotics.⁶⁸ Importantly, the antibiotic helps to prevent the formation of a bacterial biofilm, which if established usually means that the implant has to be removed.⁴⁴

A systematic review and meta-analysis of the additional benefit of local prophylactic antibiotic therapy for infection rates in open tibia fractures treated with intramedullary nailing showed that when local antibiotics were administered as adjunctive prophylactic therapy, the rate of infection was lower for all Gustilo-Anderson grades of tibia fractures.⁵ In particular for the more severe GAIII fractures, adding local antibiotics to systemic antibiotic prophylaxis reduced the infection rate from 14.4% to 2.4%. For the most severe cases among those (GAIII B&C) the incidence of infections fell from over 31% with systemic antibiotics only to under 9% with the addition of local antibiotics.⁵

However, it has been stressed in the literature that the optimal local antibiotic delivery system should have the ability to provide a concentration of antibiotic at a level that i) is above the minimal bactericidal concentration in order to prevent bacterial resistance, ii) is sufficient to overcome remaining pathogens and iii) does not affect bone healing and iv) reduces the risk of systemic toxicity.^{7,69} Currently available options do not always manage to meet these objectives and may pose additional challenges. For instance, the antibiotic release from antibiotic-impregnated PMMA cement beads that are commonly used to fill the dead space resulting from debridement is considered to be insufficient, creating the potential for PMMA cement beads to act as foreign body for bacterial colonization.^{9,69} In vitro research showed that antibiotic release fell below the detection limit after one week and that a total of only 4-17% of the incorporated antibiotic (gentamicin) was finally released.⁷⁰ Moreover, a disadvantage of PMMA cement beads is that they

are non-degradable and require a second surgery for removal, which may raise the risk for acquiring a new intraoperative infection.^{7,9,69}

There is general consensus that novel preventive and therapeutic options are needed against implant-related infections.⁸⁻¹⁰ Ongoing research is assessing different options such as strategies that will target and reduce the already formed biofilm, antibacterial strategies and strategies looking into the modification of orthopaedic implants.⁸ In this context there has been particular reference to implant coatings and their potential in addressing implant-related infection.⁸⁻¹⁰

EXPERT TIBIAL NAIL PROtect

ETN PROtect is an intramedullary (IM) nail intended for the fixation of fractures. It is coated with a fully resorbable poly(D,L-lactide) (PDLLA) coating, in which particles of the antibiotic Gentamicin sulfate are embedded (minimal for the smallest nail, 15.3 mg and maximal for the largest 65.2 mg). The PROtect Coating

is designed to enhance safety for high risk patients by preventing bacterial colonization on the implant surface. The PROtect Coating is designed as a supplement to systemic antibiotic prophylaxis, which is routinely used as a perioperative measure for prevention of surgical site infections.



Enhanced Patient Safety

Designed to enhance safety for high-risk patients

Targeted Protection

Developed to deliver targeted protection against localized infection

Clinically Proven

Clinical experience with supporting evidence

Enhanced Patient Safety

Designed to enhance safety for high-risk patients

ETN PROtect is developed for patients with a closed epiphysis suffering from fractures in the tibial shaft as well as metaphyseal and certain intraarticular fractures of the tibial head and the pilon tibiae, the same indications covered by the Synthes Expert Tibial Nail (uncoated).⁷¹

However, certain patients will be at an increased risk of an infection based on factors related to the type and severity of their injury and their overall health status.^{4-6,41,43}

Based on key factors that have been associated with an increased risk of infection among patients with tibia fractures, cases that could benefit particularly from the PROtect Coating technology include:

- All open fractures (Gustilo-Anderson Grade I to III)
- Secondary nailing (nail to nail and external fixator to nail)
- Polytrauma
- Immunodeficiencies such as diabetes mellitus, obesity, alcohol abuse, smoking, etc.

Targeted Protection

Developed to deliver targeted protection against localized infection

The addition of locally delivered antibiotics to systemic antibiotic prophylaxis has been shown to create sufficiently high antibiotic concentration on the tissue-implant surface and potentially reduce infection rates.⁵

The PROtect Coating fulfills the requirements of local delivery antibiotic systems as it releases gentamicin sulfate, known for its broad spectrum, immediately after implantation into the surroundings of the implantation site bacteria for approximately 2 weeks, with 80% being released within 24 hours.⁷² This is important as it is known that a prolonged release at rather low dosages is more likely to favor the emergence of resistant bacterial strains.⁶³ It releases high doses of antibiotics where systemic administration can hardly reach, with the local concentration being up to 1000 times higher than in systemic application.⁶⁷ While creating high concentrations, the release of the antibiotic agent is highly local with no detectable systemic side effects.⁷³ The PROtect Coating is completely resorbed after approximately 6 months.*

PROtect Coating is designed to prevent bacterial colonization on the implant surface, which is considered as an important support asset to reduce the risk of infection.⁷³

*Resorption time may vary depending on patient specific conditions.

Clinically Proven

Clinical experience with supporting evidence

The PROtect Coating has been applied to ETN PROtect and its predecessor the Unreamed Tibia Nail (UTN) PROtect. Clinical experience has demonstrated the performance and safety of the two intramedullary nails featuring the PROtect Coating.

A literature search was performed using PubMed, OVID and QUOSA to identify studies performed using ETN PROtect. The scope of the search included studies on UTN PROtect, as it has an identical antibiotic coating to ETN PROtect and a similar nail design*, and therefore is expected to have a similar effectiveness and safety profile. Studies were only included if the use of ETN or UTN PROtect was on label. As a result of this, four relevant studies were identified and summarised; two single centre case series studies and two case studies.^{11,12,74,75}

Patients with different types and severity of injuries were included across these studies: Fuchs et al. 2011 reported on patients with both closed and open fractures GA I-III, Metsemakers et al. 2015 on patients with open frac-

tures grades GA II-III, Raschke et al. 2010 and Raschke et al. 2014 on one case of a severe GAIII C fracture each. The cohorts studied by Fuchs et al. 2011 and Metsemakers et al. 2015 included patients with multiple injuries (polytrauma patients) and complex revision cases.

The primary outcomes of interest reported were the development of a deep infection and bony union following fracture fixation with the PROtect coated nail. An overview of the results is presented in table 5. In all four studies, none of the patients developed a deep wound infection. Only Fuchs et al. reported a superficial infection, which was treated with debridement.

Union outcomes were reported at different time points across the studies. In 3 out of 4 studies, full fracture healing was observed within a year in all patients.^{12,74,75} Despite the absence of a deep infection, Metsemakers et al. 2015 found that 25% of patients (4 out of 16) suffered from non-union.¹¹ The author attributed the incidence of non-union to the complex pattern of injury of these patients.

	Fuchs et al., 2011 ⁷¹	Metsemakers et al., 2015 ¹¹	Raschke et al., 2014 ¹²	Raschke et al., 2010 ⁷²
Sample size	n=19	n=16	n=1	n=1
Intramedullary nail	UTN PROtect	ETN PROtect	ETN PROtect	UTN PROtect
Non-union	0/19 after 3 months	4/16 (timing not reported)	0/1 a year after trauma	0/1 after 3 months
Deep wound infection	0/19	0/16	0/1	0/1

Table 5: Infection and union outcomes following the implantation of ETN or UTN PROtect.

Adverse events were reported, but none of the adverse events was reported to have causative relationship with ETN PROtect Coating.^{12,75} In the single centre case series several unrelated adverse events recorded. Fuchs et al. reported reoperation in three patients due to serious adverse events including a thromboembolic event, hip pain and issues with local wound healing.⁷⁴ A quarter

of the patients in the study by Metsemakers et al underwent reoperation due to fracture non-union.¹¹

* The main difference between these two implants are the locking options, which allow a more flexible use of ETN compared to UTN and the treatment of a broader range of indications, specifically, fracture closer to the joint areas.⁷⁶

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