The usage of antibiotics in bone surgery

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The Usage of Antibiotics in Bone Surgery

GRADUATE THESIS

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ABBREVIATIONS

MRSA – methicillin-resistant Staphylococcus aureus

SSI – Surgical site infection

CDC – Centre for Disease Control and Prevention

6-APA – 6-amino-penicillanic-acid

PJI – Periprosthetic joint infection

RNA – Ribonucleic acid

DNA – Deoxyribonucleic acid

CSF- Cerebrospinal fluid

I.V. - Intravenous

MRSE – methicillin-resistant Staphylococcus epidermidis

BMI – Body Mass Index

Summary

The Usage of Antibiotics in Bone Surgery

Patrick Tschechne

The discovery of antibiotics has drastically changed modern medicine and everyday human life. Even though extraordinary discoveries have been made perioperative infections are still commonly encountered in clinical practice. Deep infections such as septic arthritis, osteomyelitis and periprosthetic joint infections pose great difficulties to practising surgeons and increase the financial burden for health care systems across the globe. Multiple antibiotic regimens are commonly used where bone surgery is performed. Cephalosporins such as cefazolin are routinely administered in surgical theatres around the world, as a measure of prophylaxis to surgical site infections. Nevertheless other antibiotics are also frequently indicated. Due to a rise in multidrug-resistant micro-organisms worldwide, glycopeptide administration has over time increased markedly. For instance vancomycin may nowadays be used in clinical settings where methicillin-resistant Staph. aureus (MRSA) is often encountered. Despite existing clinical guidelines, research is still needed to keep the surgical community up-to-date during the combat of perioperative infections.

Key words: Antibiotics, Bone Surgery, Perioperative Surgical Prophylaxis, Surgical Site Infections, MRSA

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1. Introduction

In modern medicine antibiotics are used in everyday clinical practice and play according to medical progress an increasingly important role where state-of-the-art bone surgery is performed.

Not long ago Surgical Site Infection (SSI) has been defined by the united states centre for disease control and prevention (CDC) as an “infection, connected to an operative procedure, that occurs at or near the site of surgical incision within 30 days of the procedure or within 90 days if prosthetic material was implanted“.[1]

Although for instance in USA surgeons obey elaborated rules of prevention, nosocomial infections rank among the ten leading causes of death in the United States of America. Accounting for over 35% of hospital acquired infections, surgical site infections are the most common cause of nosocomial infections. Approximately 2 to 5 % percent of over 30 million surgical patients yearly suffer from a SSI. [2, 3]

This leads to the fact that SSIs can have a remarkable influence on the patients treatment plan and are associated with substantial morbidity and mortality increase, higher treatment intensity, higher costs and extended length of stay.[4, 5]

In a paired case-control study of SSI after orthopaedic procedures in the year 2002 it was shown that, the median length of stay in the hospital was prolonged by 14 days, re-hospitalization rates were doubled, and the total costs were over 300 percent higher.[6]

Looking at those facts, one has to conclude that Antibiotic Administration must be recognized as highly influential to the outcome of surgical interventions, whose results can be largely affected by postoperative Surgical site infections.[7] So decreasing the rate of postoperative surgical site infections [7] by Antibiotic Administration plays a key role in modern surgery.

Therefore to optimize the progress of modern surgery, we have no alternative but to further

investigate antibiotic properties, antibiotic administration and the outcome of treatment regimens as well as providing continuous education to every level of clinical professional involved in surgical interventions, to reach the decrease in the number of perisurgical infections to a minimum.

In this review an overview of commonly used antibiotics in bone surgery will be given and results from published studies will be compared to provide an up-to-date understanding of the contemporary perioperative antibiotic regimens.

It will focus on several essential questions:

- why antibiotics are administered perioperatively,
- why certain antibiotic administration is preferred,
- when antibiotics should be administered,
- why antibiotic regimens vary in different clinical settings.

2. Antibiotics

2.1 History of Antibiotics

In the past medicine possessed no reliable tool against bacterial infections and they were considered permanently threatening the lives of humans. Nowadays the discovery and development of penicillin and the following antibiotics has changed the general perception and attitude towards bacterial infections.
Nevertheless in modern medicine bacteria are ubiquitous and constantly evolving and this constant change in bacterial organisms renders our antibiotic agents over time less effective.

Today one can say that the discovery of antibiotics possibly changed the capacity of modern pharmacology and medicine more than any other therapeutic intervention. Through its immense and immediate effect on mortality rates it has altered everyday life and human health.

The beginnings of modern pharmacology are marked by Oswald Schmiedeberg (1838-1921), who has broadly been accepted as the founder of modern pharmacology. In 1866 Schmiedeberg received his medical doctorate at the University of Dorpat, Latvia and thereafter worked in Dorpat under Professor Buchheim a well-known scientist at his time. Schmiedeberg then became Professor of Pharmacology in 1872 at the University of Strasbourg, where his scientific reputation attracted students from many other cities. During his 46 year long stay at the University of Strasbourg, Schmiedeberg educated and trained many men that would go on to become professors at other German universities. Up to world war II the predominance of the German pharmaceutical industry was largely based on Professor Schmiedebergs´ scientific and educational efforts.[8]

One of Prof. Schmiedebergs´ main merits was the introduction of experimental pharmacology as a biological science. He thereby established the foundation for the development of further pharmacological progress.[9] This would ultimately result in contemporary pharmacology including the development of antibacterial agents.

This was the foundation that influenced the way of scientific thinking from that time on and made it possible that in 1929 the most important and accidental breakthrough in antibiotic research took place. It was a discovery that would change the world, when Sir Alexander Fleming published the observation that a penicillium mould inhibits the growth of various bacteria. This discovery is widely accepted as the beginning of the modern era of antibacterial drug discovery.[10]

Years after Fleming´s Discovery, Sir Howard Walter Foley and Ernest Boris Chain, decided to investigate the clinical potential of penicillin. This ultimately resulted in a shared Nobel Prize for Medicine in 1945 for Fleming, Foley and Chain.[11]

From that time on scientists all over the world started to work on the ground prepared by the findings of penicillin effects. So the discovery and outstanding effects of penicillin triggered a further search for antibiotic producing organisms. Most of the discoveries following penicillin were based on soil surveys. The sample collection in Soil surveys is aimed at obtaining a wide variety of samples. These samples must then be cultivated and examined for possible antibiotic activity. This boost of investigations yielded a wide range of substances.[12] Major natural antibiotics are given with the date of discovery in Table 2.1.1

Table 2.1.1 : Date of discovery and source of natural antibiotics adapted from Finch, R.G., et al.[13]

Name		Date of discovery	Microbe
Penicillin		1929–40	Penicillium notatum
Tyrothricin	Gramicidin Tyrocidine	1939	Bacillus brevis
Griseofulvin		1939 1945	Penicillium griseofulvum Dierckx Penicillium janczewski
Streptomycin		1944	Streptomyces griseus
Bacitracin		1945	Bacillus licheniformis
Chloramphenicol		1947	Streptomyces venezuelae
Polymyxin		1947	Bacillus polymyxa
Framycetin		1947–53	Streptomyces lavendulae
Chlortetracycline		1948	Streptomyces aureofaciens
Cephalosporin C, N and P		1948	Cephalosporium sp.
Neomycin		1949	Streptomyces fradiae
Oxytetracycline		1950	Streptomyces rimosus
Nystatin		1950	Streptomyces noursei
Erythromycin		1952	Streptomyces erythreus
Oleandomycin		1954	Streptomyces antibioticus
Spiramycin		1954	Streptomyces ambofaciens
Novobiocin		1955	Streptomyces spheroides Streptomyces niveus
Cycloserine		1955	Streptomyces orchidaceus Streptomyces gaeryphalus
Vancomycin		1956	Streptomyces orientalis

Name	Date of discovery	Microbe
Rifamycin	1957	Streptomyces mediterranei
Kanamycin	1957	Streptomyces kanamyceticus
Nebramycins	1958	Streptomyces tenebraeus
Paromomycin	1959	Streptomyces rimosus
Fusidic acid	1960	Fusidium coccineum
Spectinomycin	1961–62	Streptomyces flavopersicus
Lincomycin	1962	Streptomyces lincolnensis
Gentamicin	1963	Micromonospora purpurea
Josamycin	1964	Streptomyces narvonensisvar.josamyceticus
Tobramycin	1968	Streptomyces tenebraeus
Ribostamycin	1970	Streptomyces ribosidificus
Butirosin	1970	Bacillus circulans
Sissomicin	1970	Micromonospora myosensis[13]
Rosaramicin	1972	Micromonospora rosaria

Table 2.1.1 does not represent all the antibiotics discovered but describes most antibiotics to which further discoveries were related.

Interestingly all ensuing marketed antibiotics, at least to the early 2000s, have predominantly been semi-synthetic or synthetic derivatives and modifications of pre-existing antibacterial substances. Although a great deal of the next-generation agents showed a noteworthy clinical applicability in the treatment of bacterial infections, they did not constitute genuinely new mechanistic classes of antibiotics.

A great example for the discovery of antibiotics in the late 1900s is the discovery of azithromycin

by a research group of the pharmaceutical company PLIVA in Zagreb, Croatia. In 1981 azithromycin was patented and had global impact ever since. While azithromycin constituted great innovation and applicability, especially due to its slow excretion, it was still a derivative of erythromycin.

The lack of new mechanistic classes during this period proposes that successes in the discovery and development of new antibiotic classes have been relatively scarce.

An explanatory concept to this stagnation is that at times the discovery of large quantities of useful antibiotics, during the twentieth century, has been viewed to set an end to the era of demand for new antibiotics. This interpretation was based on an extensive decrease in the specific mortality, given bacterial infections are the cause of death.

Nevertheless opinions have changed and at present we know that bacteria are very dynamic organisms adapting to environmental influences and resisting xenobiotics, including antibacterial agents. This leads to the progressive increase in bacterial resistance to antibiotics commonly used nowadays. In fact there is no doubt on the demand of continuous research aiming at the discovery and development of new antibacterial agents to be necessary. [14] [15] [16] [17]

2.2 Classes of antibiotics commonly used in bone surgery

2.2.1 β-lactam Antibiotics

2.2.1.1 Penicillins

As described above Penicillin was discovered by Sir Alexander Fleming in 1929. Penicillin, as well as all its derivatives, are comprised of 6-amino-penicillanic-acid (6-APA), which is composed of a beta-lactam-ring and thiazolidine. All penicillins act by disruption of the bacterial cell wall.

The drugs attach to the penicillin-binding proteins on susceptible bacteria and inhibit the enzyme transpeptidase. Transpeptidation is the process in which peptide chains are cross-linked within the peptidoglycan layer of the bacterial cell wall. The inhibition of transpeptidation leads to instabilities in the cell wall and a discrepancy in the hydrolytic processes and processes of cell wall formation. These processes are part of the constant remodelling taking place in bacterial cell walls and ultimately lead to lysis of the cell by osmotic pressure.

Benzylpenicillin or penicillin G and phenoxymethylpenicillin or penicillin V were the first penicillins. These penicillins occurred naturally and are still in clinical use. Main disadvantages of benzylpenicillin are β-lactamase-susceptibility and absorptive qualities. Penicillin G shows inadequate activity against β-lactamase-producing bacteria. Furthermore penicillin G is poorly absorbed through the gastrointestinal tract and therefore has to be administered by injections.[18]

One direction of scientific work for the further development of Penicillin had the aim to develop derivatives of the first penicillins by adding different substituents to the 6-APA. Through these processes it was possible to create antibacterials with broader range and higher activity against β-lactamase-producing-bacteria.

Broad-spectrum penicillins such as the amino-penicillin amoxicillin possess a wider activity against gram negative organisms, such as Salmonella typhi or coli bacteria.[19]

The research on isoxazolylpenicillins was driven by clinical problems when staphylococci started producing a penicillinase and thereby became resistant to penicillin G and penicillin V. An answer to the problem was presented in 1959 when Peter Doyle and John Nayler created methicillin which was not inactivated by the penicillinase of staphylococci but showed adequate activity against staphylococci.

The disadvantage of methicillin was that it inconveniently had to be given by injection and therefore research continued aiming for a derivative that could be administered orally. The synthesis of oxacillin and cloxacillin, which can be administered orally, took place two years after the marketing of methicillin and enabled broader use. Modifications to oxacillin and cloxacillin then gave rise to dicloxacillin and flucloxacillin with the advantage that if given orally dicloxacillin as well as flucloxacillin can produce better concentrations in the bloodstream in comparison to their progenitors.[20]

Today it can be observed that commonly chosen isoxazolylpenicillins in clinical use are oxacillin, cloxacillin, dicloxacillin and flucloxacillin. This series of semi-synthetic penicillins possesses acid stability and effectiveness against gram-positive bacteria as well as resistance to penicillinase. Isoxazolylpenicillins are absorbed when administered per os or by injection and the efficacy is significant and established against penicillin-resistant staphylococci, other gram-positive bacteria and streptococcal infections.

The chemical properties and antimicrobial activities are similar for cloxacillin, oxacillin and dicloxacillin. However there are differences such as less effectivity of cloxacillin against pneumococcal infections and oxacillin´s lower effectivity against penicillin-resistant staphylococcal infections, when they are compared to one another.[21]

Generally absorption of penicillins depends on acid stability and adsorption to foodstuff in the gut. Penicillins are lipid insoluble and therefore do not enter human cells and cannot cross an intact

blood-brain-barrier. Nevertheless penicillins distribute into joints, bile, saliva, breast milk, pleural and pericardial spaces. Penicillins even extend across the placenta and can be administered orally, with the exception of penicillin G, intravenously and intramuscularly. The elimination of Penicillins is predominantly renal.

Regarding the usage of penicillins we can observe that they are still used for sensitive bacteria and certain infections. Due to a high degree of bacterial resistance, sensitivity testing may be adequate on the individual level with regards to local settings. Penicillins, with regard to sensitivities, are for instance still used for bacterial meningitis, bacterial pharyngitis and skin and soft tissue infections. Occasionally it may be indicated to start penicillins empirically while laboratory results are pending and the probability of penicillin susceptibility is high.

Adverse effects of penicillins are mainly hypersensitivity reactions, leading to fever as well as rashes and must be thought of, if the patient experiences discomfort after drug administration. The gastrointestinal flora is also altered if penicillin is given perorally and can lead to gastrointestinal complaints and suprainfection for instance by clostridium difficile leading to pseudomembranous colitis. Furthermore it has to be kept in mind that anaphylactic shock can occur, granting great importance to anamnestic documentation of penicillin allergies.[18]

2.2.1.2 Cephalosporins

According to the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection (PJI) a first or second generation Cephalosporin should be administered for routine perioperative surgical prophylaxis.[22]

Cephalosporins belong to the class of β-lactam antibiotics. The first isolation of cephalosporins was made from Cephalosporium fungus. Their biochemical effectiveness results from the fact that

Cephalosporins bind to the β-lactam-binding proteins and form covalent bonds with penicillin-binding proteins. According to this they are capable of inhibiting the last transpeptidation step necessary in the synthesis of bacterial cell wall peptidoglycan.

Nowadays a large amount of different cephalosporins are in clinical use. This includes semi-synthetic broad-spectrum cephalosporins:

- second-generation drugs such as cefuroxime,
- third-generation drugs such as ceftriaxone, cefixime and cefotaxime.

Third generation Cephalosporins have in clinical practice widely replaced first-generation cephalosporins such as cefazolin.[18] However in perioperative surgical prophylaxis cefazolin is still widely used.[23]

As a reaction to widespread cephalosporin use, plasmid-encoded and chromosomal β-lactamases have led to a higher degree of resistance to cephalosporins. Likewise changes to the membrane proteins or mutations in the binding-site proteins can result in diminished drug penetration and thereby also cause resistance.

Cephalosporins are largely given parenterally, intramuscularly as well as intravenously. Cephalosporins are in most cases excreted by tubular secretion in the kidney. Although some cephalosporins such as ceftriaxone are up to 40% eliminated in the bile.

Some adverse effects may occur while being treated with cephalosporins. As with penicillins, adverse effects have to be monitored and careful documentation of cephalosporin allergy must be undertaken. Allergic reactions to cephalosporins have been reported as well as nephrotoxicity and drug induced alcohol intolerance. Hypersensitivity reactions resemble allergic reactions to penicillin individuals with penicillin allergy are also at higher risk of having allergic reactions to cephalosporins. Diarrhoea is another common adverse effect and can be caused by Clostridium difficile.[18]

2.2.2 Glycopeptides

Vancomycin, possibly the most important representative of the Glycopeptide antibiotics, was discovered in the 1950s. Glycopeptides consist of two sugars and an aglycone moiety made of heptapeptides. They are produced by the species Streptococcus orientalis and amycolatopsis orientalis. Similarly to β-lactam-antibiotics Glycopeptides work by interfering with cell wall synthesis. By inhibition of the transglycosylation and transpeptidation, glycopeptides prevent the elongation of peptidoglycan and cross-linking. This leads to instabilities in the cell wall similar to those produced by penicillins and ultimately leads to cytolysis.

Glycopeptides are relatively large molecules with a molecular weight of 1500. Due to the size glycopeptide antibiotics are unable to penetrate the outer cell membrane of gram-negative bacteria, limiting their activity to gram-positive organisms. Likewise they cannot penetrate inside cells, and are therefore limited to extracellular targets.[24]

Teicoplanin is another member of the glycopeptide antibiotic class.

The activity against gram-positive cocci is heterogeneous even though the basic mode of action is the same throughout the glycopeptides. This is mainly due to structural differences outside the heptapeptide backbone.[25] Research on these structural differences lead to the development of lipoglycopeptides, which show advanced antibacterial activity by dimerization and binding to bacterial membranes simultaneously.[26]

Vancomycin itself acts only on dividing cells and relatively slow, if compared in vitro or in vivo with penicillin. Additionally vancomycin is not absorbed in the gastrointestinal tract and its only oral indication therefore is pseudomembraneous colitis caused by clostridium difficile. Parenteral administration is only possible intravenously. It should be considered that vancomycin should be administered continuously due to its plasma half-life of about eight hours. If given parenterally vancomycin has a wide distribution throughout the body. Teicoplanin, contrary to vancomycin, can

be administered once a day and intramuscularly as well as intravenously.

The most important indications for vancomycin are infections caused by methicillin-resistant staphylococci. Most pathogenic, β-lactamase producing staphylococci are susceptible to the action of vancomycin. This includes the staphylococci resistant to nafcillin and methicillin. Nevertheless Vancomycin is less effective, if compared to traditional treatment, against staphylococci if these are susceptible to methicillin.

Glycopeptides are mainly excreted by the kidney hence clearance of the drug is proportional to creatinine clearance and the dosage should be individually calculated if renal clearance is reduced.

Adverse effects can be seen in about 10% of patients receiving a glycopeptide.

The majority of adverse effects are minor such as chills and fever. Vancomycin can also lead to phlebitis at the site of injection. A more common side effect is the infusion-related flushing due to histamine release called the „red man“syndrome. Ototoxicity and nephrotoxicity are serious but rare site effects if a glycopeptide is given alone. However the risk of ototoxicity and nephrotoxicity increases if other drugs with the same side effects are given simultaneously, for example aminoglycosides.[27]

2.2.3 Rifamycin

According to the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection a rifampicin regimen is to be administered in gram-positive PJI.[22]

Rifampin or rifampicin is a member of the rifamycin antibiotic class. Rifampin is a semi-synthetic derivative of rifamycin. Rifamycin is produced by nocardia mediterranei. In Milan, Italy research on rifamycins yielded rifampin (N-amino-N´-methylpiperazine) which was introduced into clinical use in 1968.[28] [28]

Rifampin acts by inhibiting RNA synthesis. It binds to the prokaryotic enzyme DNA-dependent

RNA polymerase while it cannot bind to the eukaryotic RNA polymerases. Therefore it does not affect human transcription.

Oral administration of rifampin leads to good absorption and a wide distributes through the body, spreading through tissues, abscesses and into phagocytic cells. It also spreads readily to body fluids leading to orange discolourations of sweat, saliva, sputum, urine and tears as well as spreading to the CSF.[18] After being mainly excreted into bile and undergoing enterohepatic circulation, it is mostly excreted in faeces. Therefore renal insufficiency has no influence on the dosage.[27] Induction of hepatic enzymes, leads to a decrease in half-life during the course of treatment. The initial half-life is 1-5 hours.

Rifampin shows adequate activity against most gram-positive and many gram-negative cocci. Due to its ability to enter cells it also shows significant effect on intracellular micro-organisms such as mycobacteria and chlamydia. It is therefore a powerful anti-tuberculosis drug. Rifampin is also used in combination therapy to eradicate staphylococcal carriage, as well as treatment of staphylococcal osteomyelitis.

Adverse effects are relatively rare. Skin eruptions, fever and gastrointestinal symptoms are most frequent. Occasionally rashes, thrombocytopenia or nephritis can be seen. Cholestatic jaundice and liver damage was seen in a very small group of patients.

As a result of hepatic enzyme induction, the degradation of other drugs metabolised in the liver, is accelerated. Drugs faster metabolised are for instance glucocorticoids, warfarin, oral anti-diabetics and oral contraceptive pills, meaning their oestrogen component. Rifampin is also contraindicated during the first trimester of gestation and during lactation.[18, 27]

2.2.4 Quinolones

According to the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infection fluoroquinolones should be administered in gram-negative PJI.[22]

Quinolones were discovered in 1962 when Lesher et al. accidentaly discovered nalixidic acid as a by-product of the chloroquine synthesis. Modifications to the quinolone nucleus gave rise to altered antimicrobial activity, most importantly the addition of fluorine allowed penetration into bacterial cells and showed activity against staphylococci. Moreover the addition of a cyclopropyl group, gave rise to ciprofloxacin, which shows increased activity against gram-positive and gram-negative bacteria.

Quinolones inhibit at least one enzyme of the topoisomerases. Topoisomerases are necessary during replication and transcription of DNA. The enzyme group, particularly topoisomerase 2 or DNA gyrase, alleviates the strain on DNA strands to enable replication and transcription to proceed.

By inhibiting these enzymes fluoroquinolones block DNA synthesis and growth of the bacteria cannot occur.[29]

Quinolones are categorized into four generations based on their in vitro activity. The first-generation shows adequate activity to aerobic, gram-negative bacteria but poor efficacy against aerobic, gram-positive bacteria. Nalidixic acid, oxolinic acid, pipedemic acid are some first-generation quinolones.

Second-generation quinolones have increased activity against aerobic, gram-positive bacteria and against gram-negative bacteria. Introduced in the 1980s, they still showed poor activity against anaerobic bacteria. Norfloxacin, the first fluoroquinolone, ciprofloxacin, levofloxacin and oflofloxacin are some of the second-generation quinolones.

Third-generation fluoroquinolones show greater effect on anaerobic bacteria as well as gram-positive bacteria, especially pneumococci. Grepafloxacin, temafloxacin are some third-generation

fluoroquinolones.

Fourth-generation fluoroquinolones possess higher activity against anaerobes and pneumococci. Trovafloxacin, moxifloxacin and clinafloxacin are some fourth-generation fluoroquinolones.

Fluoroquinolones are still indicated for a great deal of infections, in example ciprofloxacin is approved for bone and joint infections, skin and skin-structure infections and numerous other infections.[30]

Adverse effects are rarely seen when fluoroquinolones are given. Most commonly skin rashes, nausea, vomiting and diarrhoea have been reported. Fluoroquinolones may lead to arthropathies in growing cartilage. Due to inhibition of P450 enzymes ciprofloxacin is seen to have interactions with theophylline, which can result in theophylline toxicity.[18]

3. Penetrance to bone of antibacterial agents

In the past it was accepted opinion that the majority of antimicrobials produce similar concentrations in tissues and plasma, nearly attaining an equilibrium.[31] However some studies have shown concentrations at the effect site to differ from the corresponding concentrations achieved in serum.[31, 32]

The antibiotic concentrations measured in bone depend on time and mode of administration, as well as the microbiological assay and sample used for measurements. Hence variations can be observed in reported values of different studies.[33]

The diffusion of antibiotics into bone can be subdivided in three classes:

- Good diffusion, being over 30% diffusion. Substances that showed good bone diffusion were fluoroquinolones, teicoplanin and rifampin.
- Moderate diffusion, showing diffusion of 15%-30%. Substances that showed moderate bone diffusion were ureidopenicillins, 2nd and 3rd generation cephalosporins and vancomycin
- Low diffusion into bone tissue, showing less than 15% diffusion. Substances that showed low diffusion were penicillin M and first generation cephalosporins.[34]

However cephazolin showed bone concentrations significantly above the minimum bactericidal concentrations for Staph. aureus and some gram-negative bacteria.[33]

Unfortunately guidelines for the research and evaluation of bone penetration studies are still needed[35] and moreover a clear association between increased concentrations of antibiotics in bone and clinical outcome has not been shown yet.[36]

Conclusively the choice of antibiotic should be governed by patient, microbiological and surgical factors on an individual basis, involving the clinician and the medical microbiologist.[37]

4. Current usage of antibiotic treatment in bone surgery

4.1 Routine perioperative surgical prophylaxis

To be optimal, routine surgical prophylaxis should posses certain qualities. Typically these qualities include, that:

Firstly an adequate drug concentration is maintained in the wound, serum and tissue during the whole length of operation. Special awareness has to be maintained during the period when the incision has not been closed yet and is at risk of bacterial contamination.

Secondly the antimicrobial agent should be safe for the patient and show adequate activity against frequent pathogens encountered in the given type of operation. Whilst showing great activity against the probable pathogens, the drug should show lowest possible activity against the normal bacterial flora.

Thirdly the agent should also be carefully chosen with regard to its promotion of bacterial resistance.

Fourthly the economic burden to the hospital and health care system should be taken under consideration.[38]

Bearing all these factors in mind common consensus is, that routine perioperative surgical prophylaxis should consist of a first- or second-generation cephalosporin, such as cefazolin or cefuroxime.[22, 39]

These drugs possess great activity against the majority of the causative agents for postoperative wound infections and a good safety profile.[40] First- and second-generation cephalosporins also show excellent distribution in synovium, muscle and bone.[41] In addition more advanced agents and treatment regimens of higher cost need to be reserved for upcoming pathogens and drug-resistant

micro-organisms.[22]

The serum half-life of cefazolin is 1.8 hours, with a mean bone concentration of 5.7 micrograms per gram of bone and a mean synovial fluid concentration of 24.4 micrograms per millilitre of synovial fluid. Minimal bactericidal concentrations are rapidly achieved by these cephalosporins, for covered non-MRSA organisms.[42]

As demonstrated by clinical studies the incidence of deep infections, after hip arthroplasty, can be reduced from 3.3% to 0.9% by the administration of cefazolin.[43]

In another clinical trial, efficacies of three day cefazolin versus one day cefuroxime administration were compared. The goal was to determine the impact on postoperative wound infections. Ultimately the regimens did not show statistically significant differences.[44, 45]

In 2009 a study showed that in Scandinavia cloxacillin is most frequently used for surgical prophylaxis. It was shown that 99% of Staph. aureus and 80% of coagulase-negative Staphylococcus strains, in a cohort study of patients undergoing total joint arthroplasty in Sweden, were susceptible to cloxacillin.[46] Thus can be concluded that isoxazolylpenicillins are an appropriate alternative to cephalosporins for routine surgical prophylaxis.[22]

Routine surgical prophylaxis should be administered 30 minutes before incision and for the duration of one day. Prolonged application of prophylactic antibiotics can promote bacterial resistance and lead to higher costs.[47]

For surgical procedures of long duration additional administration of antibiotics should be considered. The duration of surgery as well as blood loss, and fluid resuscitation are factors to consider in evaluating re-administration. As a general rule an additional dose of prophylactic antibiotic should be administered when the duration of surgery exceeds two half-lives of the prophylactic agent.

Guidelines therefore calculated re-dosing intervals for several antibiotics to be:

- every 2 to 5 hours for cefazolin
- every 3 to 4 hours for cefuroxime
- every 3 hours for isoxazolylpenicillin
- every 3 to 6 hours for clindamycin
- every 6 to 12 hours for vancomycin.

In case of large blood loss the prophylactic agent may be lost in significant quantity, altering concentrations to inadequately low levels. Therefore it has been established that an additional dose of antibiotic should be given when blood loss is greater than two litres. Similarly changes in drug concentration can occur by high volume fluid resuscitation. Intraoperative re-administration of antibiotics has been established to be indicated if more than 2 litres of fluid have been given to the patient.

These events should be observed independently and additional doses should be given as soon as one parameter is met.[22]

4.2 Alternatives to routine perioperative surgical prophylaxis

If routine prophylaxis cannot be given, a valid option is the usage of vancomycin or teicoplanin. Vancomycin has a shorter half-life and shows higher incidences of adverse effects, if compared to teicoplanin.[48] Another disadvantage of vancomycin lies in the need of serum monitoring to ensure therapeutic concentrations. Furthermore the administration of teicoplanin is less complicated due to its prolonged half-life and the option of intramuscular injections. Consequently teicoplanin may be an advantageous choice.[49]

A randomised controlled trial compared the administration of a single IV bolus of teicoplanin with the administration of 5 doses of cefazolin in a 24 hour period. Surgical wound infections and

adverse effects were observed in both groups and no significant differences were reported.[50]

Governed by the increasing occurrence of MRSA and methicillin-resistant Staph. epidermidis (MRSE) the introduction of glycopeptides, such as teicoplanin and vancomycin, may be reasonable in clinical settings with high MRSA and MRSE frequencies.[51] Major drawback of teicoplanin is its unavailability in certain countries.

4.3 Prophylaxis in patients with penicillin allergy

A patient undergoing bone surgery with a documented anaphylactic penicillin allergy is to be given clindamycin, vancomycin or teicoplanin for surgical prophylaxis. If MRSA rates are low, in the specific clinical setting, clindamycin should be preferred if a contraindication such as a true β-lactam allergy has been established.[22] On the other hand if a non-life threatening penicillin reaction is documented cephalosporin may be given. Data suggests cross-reactivities of penicillins and cephalosporins to be lower than historically believed, rendering cephalosporins safe for prescription.[52] If unsure a skin prick test can be used to evaluate whether the patient has a true β-lactam allergy. A negative penicillin skin test very clearly establishes that administration of the a β-lactam is safe at the time of testing.[53]

4.4 Surgical prophylaxis in patients with preexisting conditions

4.4.1 Patients with abnormal urinary screening or urinary tract infection

Patients reporting urinary symptoms, prior to planned elective arthroplasty, should undergo urinary screening. Urinary screening is indicated, because hematogenous spread of pathogens into the joints from a source elsewhere in the body, is a mechanism suggested to be causative of joint infections. Urinary symptoms can be classified into obstructive and irritative symptoms.

Obstructive symptoms, marked by pyuria, should be followed by the consultation of an urologist. The consultation is necessary ahead of surgery and delay of surgery should be considered.

Irritative symptoms such as frequency, urgency and dysuria indicate delay of surgery, if concomitantly a bacterial count over $1x10^3$/ml is observed.

Asymptomatic bacteriuria should not be a reason to delay surgery. These patients should receive adequate postoperative oral antibiotics for 8 to 10 days, if the urinary colony count is greater than $1x10^3$/ml.

As a measure to decrease postoperative Urinary tract infections a bladder catheter should be inserted immediately preoperatively and removed 24 hours after surgery.[54]

4.4.2 Patients with obesity

Preoperative antibiotics need to be weight adjusted. Due to different pharmacokinetics of antibiotics in adipose tissue and therefore obese patients doses should be adjusted to the patient’s weight under consideration of drug properties.

Dose amounts should be proportional to the patient weight. Cefazolin dosage for instance should be doubled if the patient exceeds 80kg. Therefore patients weighing under 80kg should be given 1

gram cefazolin, whereas patients weighing over 80kg should receive 2 grams of cefazolin.[22] It was shown that 2 grams of cephazolin provide adequate antibiotic levels for 4 hours even in the morbid obese (BMI 40-50kg/m^2).[55] Currently the standard recommendation for adults is to administer 2g of Cefazolin.

Clindamycin is recommended to be given in a range of 600-900mg. Dosage of vancomycin, with intact kidney function, is recommended to be 10-15mg/kg, but not exceeding 1 gram. Loading doses for vancomycin are calculated on the basis of total body weight and maintenance doses are established due to calculated creatinine clearance.[22]

4.5 Prophylaxis in patients with previous joint infection and in second-stage procedures

Septic arthritis, osteomyelitis and PJI are serious deep infections. If a history of joint infection is present in a patient scheduled for orthopaedic surgery, the preoperative antibiotics should be adjusted to cover previous causative organisms. Additionally antibiotic laden bone cement should be used if a cemented procedure is indicated.[22]

A matched case control study reported that knees undergoing total knee arthroplasty show 4.1 times higher likelihood of additional procedures if the knee was previously infected. It was also recommended that patients with evidence of infection less than one year ago should receive a two-staged procedures for total knee arthroplasty.

The recommendation to administer 4 to 6 weeks of adequate antibiotic treatment before the second procedure was given as well.[56] The risk of recurrent infection is higher in the particular case of re-implantation surgery after a two-stage procedure. In 18 patients that had failed the first two-stage revision surgeries and underwent another two-stage revision procedure, the same micro-organisms as in previous infections were found in 17 patients.[57]

An occurring recurrent infection may be caused by a new infection or by the previous causative agent. Therefore coverage of the previous as well as the most common organisms appears logical. Furthermore failure of implants has been decreased by antibiotic laden cement in patients with high risk.[22]

There are efforts undertaken to solve periprosthetic joint infections by one-stage instead of two-stage revision surgeries. One-stage revision would have a clear advantage since it would only require one surgical intervention. A prospective study found that total hip arthroplasty revision carried out as a one-stage procedure is a valid option. Selection criteria which must be fulfilled prior to surgery, are the evidence of minor bone loss and preoperative knowledge of micro-organisms. The developed decision tree could potentially decrease overall cost while assuring good standard of care.[58] Nevertheless more clinical trials will be needed for widespread acceptance.

4.6 Antibiotic coverage of war wounds

War settings pose different challenges than organized day-to-day hospital management of injuries. War injuries are mainly caused by mine, shell or artillery shrapnel. Therefore foreign material is frequently introduced into the wound. Infection may present due to inadequate management, late presentation after injury and remaining dead bone in the wound.

If a bone infection has been diagnosed there are two aspects concerning antimicrobial treatment, which need to be considered. On one hand soft tissue must be protected from mainly streptococcal and clostridial spread. This is especially true in late presenting injuries that already show signs of infection. If adequate wound excision should as well be carried out. On the other hand the antibiotic treatment should also prevent recurrence of infection. Nonetheless antibiotic treatment alone is insufficient and surgical debridement should be undertaken. All foreign material and dead tissue must be removed from the injury site to promote healing. Especially devascularized, dead bone fragments can become a reservoir for micro-organisms. Therefore recurrent infections may be

caused by dead tissue, particularly by bone left behind at the injury site. Careful evaluation of initial procedures should take place.

In circumstances where microbiological investigations are unavailable, the administration of benzylpenicillin and metronidazole is adequate. When persistent infection occurs after impeccable wound debridement a combination of cloxacillin, metronidazole and gentamicin should be given. Dosages should be: 1 gram of cloxacillin every six hours, 1.5 grams of metronidazole should in three doses daily and gentamicin should by administered every eight hours with a dose of 80 milligrams. This regimen is also indicated in patients presenting with signs of evolving sepsis. Topical antibiotics, antiseptics and antibiotic-beads are not recommended.[59]

4.7 Antibiotic treatment of open fractures

Open fractures present different problems than common closed fractures. Open fractures always imply that a communication to the external environment exists. Consequently there is a higher risk for inoculation of micro-organisms. It is generally accepted that open fracture wounds should receive emergency treatment, in order to reduce infectious complications. Open fractures are classified into 3 types:

- Type I: Open fracture with a skin wound less than 1 cm long and clean.
- Type II: Open fracture with a laceration more than 1 cm long without extensive soft tissue damage, flaps, or avulsions.
- Type III: Either an open segmental fracture, an open fracture with extensive soft tissue damage, or a traumatic amputation.[60]

The organisms contaminating open fracture wounds are of different spectrum than commonly

acquired infections in patients undergoing elective surgery. Therefore employed antimicrobial regimens should show wider activity against gram-positives and gram-negatives.

Wound microbiology should also be consulted to choose the appropriate antimicrobial treatment.

Some parameters putting patients at higher risk of infection are:

- no prophylactic antibiotics administration
- existence of resistance to antimicrobial regimen
- long duration from injury to antimicrobial treatment
- long duration from injury to surgical debridement
- closure of wound in presence of C. perfringens.

Prophylactic administration of antibiotics is recommended as soon as possible after the injury has been sustained. It should cover gram-positives for type 1 and 2 fractures. Type 3 fractures should also receive coverage of gram-negatives. For any grade a suspicion of clostridial contamination should lead to additional administration of penicillin. Therefore penicillin is generally added to the antibiotic regimen. Additionally tetanus prophylaxis should be administered, particularly if the of previous vaccination is unclear. The prophylactic antimicrobial should be administered for 24 hours in type 1 and 2 fractures and for up to 72 hours for type 3 fractures or for 24 hours after the wound has been covered.[61]

The following table sums up antibiotic agents administered in open fractures:

Table 4.7.1 Choice of antibiotic therapy in open fractures [47]

Fracture Type	Recommended antibiotic
Open type 1 and 2	First generation cephalosporin (Ancef 2g i.v. Loading dose, 1g i.v. Every 8 hours for 3 doses)
Open type 3	Third generation cephalosporin or first generation cephalosporin + aminoglycoside (gentamicin or tobramicin)
All open fractures	Add penicillin Add tetanus prophylaxis

5. Conclusion

Since the discovery of antibiotics the perception of infectious diseases has completely changed. Joint and bone infections are nowadays treated on a day-to-day basis. In the majority of cases good clinical practice of complementary surgical and pharmacological treatment protocols can bring relieve to patients.

Table 5.1. summarizes antibiotic regimens in different clinical conditions:

Table 5.1 Recommended antibiotic regimens for different indications

Indication	**Recommended antibiotic regimen**
Standard perioperative prophylaxis	First or second generation Cephalosporin Cefazolin 2g or Cefuroxime 1,5g Timing: 30 minutes before incision for 1 day
Perioperative prophylaxis in patiens with β-lactam allergy	Clindamycin 900 mg or Vancomycin 15mg/kg
Perioperative prophylaxis in obese patients	Cefazolin 3g, if weight > 120kg
Antibiotic treatment of War Wounds	According to antibiogram without microbiology: benzylpenicillin and metronidazole 1.5g/3xday Persistent infection or evolving sepsis: cloxacillin 1g/6h ,metronidazole 1.5g/3xday and gentamicin 80mg/8h
Antibiotic treatment of open fractures	Type 1/2: Cefazolin 2g i.v. Loading dose,1g i.v./8 hours for 3 doses Type 3: Third or first gen. cephalosporin + gentamicin or tobramicin + penicillin +tetanus prophylaxis

Table 5.2 summarizes properties of commonly used antibiotics:

Table 5.2 Properties of antimicrobials used in surgical prophylaxis adapted from Bratzler, D.W., et al.[62]

Antimicrobial	**Recommended Dose**	**Half-life in Adults with Normal Renal Function**	**Recommended Redosing Interval (From Initiation of Preoperative Dose)**
Ampicillin-sulbactam	3g (ampicillin 2g/sulbactam 1g)	0.8–1.3	2
Ampicillin	2g	1–1.9	2
Aztreonam	2g	1.3–2.4	4
Cefazolin	2 g, 3 g for patients weighing ≥120 kg	1.2–2.2	4
Cefuroxime	1.5g	1–2	4
Cefotaxime	1 g	0.9–1.7	3
Cefoxitin	2 g	0.7–1.1	2
Cefotetan	2 g	2.8–4.6	6
Ceftriaxone	2 g	5.4–10.9	NA
Ciprofloxacin	400 mg	3–7	NA
Clindamycin	900 mg	2–4	6
Gentamicin	5 mg/kg based on dosing weight (single dose)	2–3	NA
Levofloxacin	500 mg	6–8	NA
Metronidazole	500 mg	6–8	NA
Vancomycin	15 mg/kg	4–8	NA

When choosing an adequate antimicrobial regimen, the clinician should always abide by the standard of choosing the agent which, while being efficient, will be least likely to promote resistance. This implies reservation of more powerful antibiotics to multidrug-resistant pathogens.

Whilst showing great improvement in overall outcome, it is important to point out that antimicrobial drugs cannot replace surgical interventions and do not justify a lower standard of aseptic technique.

Some areas investigated around the world are still not unified in the approaches and measurements undertaken by researchers. For instance bone penetration is studied by many research teams around the world and different methods and materials utilized, lead to difficulties in the interpretation and comparison of reported results. Therefore guidelines for the research on bone penetration are still needed.

Even though Guidelines are in place, there are nonetheless multiple areas concerning antimicrobial treatment in bone surgery that have to be investigated. For instance globally increasing bacterial resistance, represents a problem to routine antibiotic treatment regimes. While efficacy is proven for the time being, changes in micro-organisms might render our pharmacological agents of no avail. Therefore a need for more research on patterns of evolving bacterial resistance and their implementations for future clinical guidelines is essential. Connected to this problem research to establish more evidence-based data for upcoming antimicrobials is as well needed.

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8. Biography

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Patrick Tschechne was born on the 15.12.1989 in Hamburg, Germany. After visiting the French-speaking school “Lycée Antoine-de-Saint-Exupèry de Hambourg, Hamburg, Germany“ further education was acquired at the “Gelehrtenschule des Johanneums zu Hamburg, Hamburg, Germany“ were a Latin proficiency exam was passed. Education continued at “Wilhelm Gymnasium, Hamburg, Germany“ where the German university entrance qualification was earned. Since 2008 Patrick Tschechne is a medical student at the University of Zagreb, School of Medicine. He has fluent language skills in German, English, French and Croatian. Currently Patrick Tschechne resides in Zagreb, Croatia.