The use of antibiotics in traumatology and orthopaedic surgery

Florian PURGHEL MD, PhD[a], Robert BADEA[b], MD, Radu CIUVICA[b] MD,
Andrei ANASTASIU[c], MD

[a]University of Medicine and Pharmacy "Carol Davila" Bucharest, Head of Orthopaedics
and Traumatology Department, "Bagdasar-Arseni" Emergency Hospital, Bucharest,
Romania
[b]University of Medicine and Pharmacy "Carol Davila" Bucharest, Orthopaedics and
Traumatology Department "Bagdasar-Arseni" Emergency Hospital, Bucharest, Romania
[c]Orthopaedics and Traumatology Department "Bagdasar-Arseni" Emergency Hospital,
Bucharest, Romania

ABSTRACT

The antibiotics are a very important adjuvant treatment in the infectious ostheoarticular pathology. Prevention of deep surgical wound and implant related infections in the surgical treatment of fractures and in the total hip and knee arthroplasty is made by prophylactic administration of antibiotics. The antibiotics are also used as a treatment for the ostheoarticular infections, but the antibiotic treatment is effective only together with a complete surgical treatment of the infection (infected implant or bone sequestrum removal).

The staphylococcal infections are the most frequent orthopaedic implants infections, often occur with resistant staphylococcal species and they are a major public health problem.

The characteristics of the implant material are also very important for the development of the infection, the surface of the implant influencing the bacterial colonization.

The antibiotic prophylaxis can be made according to the international protocols, but our opinion is that the antibiotic prophylaxis should be made considering the specific germs of each hospital and their antibiotic sensitivity.

INTRODUCTION

Infection is a very important problem in the orthopaedic surgery because of its continuing incidence, clinical importance and serious sequelae, the treatment being very difficult and expensive (for example, the treatment of an infected hip prosthesis costs twice as much as an aseptic revision and six times as much as the primary replacement). Rates of infection have been reduced by antibiotic prophylaxis, but the increasing number of implants used means that there are still many patients affected each year. Implants are avascular and therefore antibiotics can reach them only by diffusion from the surrounding tissues. Infection involving an implant cannot be cured simply with antibiotics and it often necessitates the surgical removal of the implant. ❏

The search for antibiotics began in the late 1800s, with the growing acceptance of the germ theory of disease, a theory which linked bacteria and other microbes to the causation of a variety of diseases.

In 1928, the British scientist Alexander Fleming discovered a substance that he named penicillin, after the Penicillium mold that had produced it, that was able to destroy a common bacterium, Staphylococcus aureus, associated with sometimes deadly skin infections. The value of penicillin in the treatment of orthopedic cases was first appreciated during World War II, in the treatment of battle casualties. By 1946, the drug had become widespread for clinical use. In the late 1940s the first penicillin resistant strains were reported, but it was not until the 1970s that antibiotic resistance was considered to be a real threat. The success of penicillin intensified

SHORT HISTORY OF ANTIBIOTICS USE IN ORTHOPAEDIC SURGERY

searches for new antibiotics that could treat other bacterial diseases, including those caused by now penicillin resistant strains. One way to combat resistance was to chemically modify penicillin, creating derivatives of the chemical, such as ampicillin, that avoided enzymatic degradation. Today, numerous penicillin derivatives exist. Because of the large number of penicillin resistant strains, ampicillin or penicillin should be added to the antibiotic regimen only when there are conditions favoring the development of anaerobic infections.

The cephalosporins are a class of β-lactam antibiotics. Cephalosporin compounds were first isolated from cultures of Cephalosporium acremonium in Italy, in 1948, and the first agent (cephalotin) was launched in 1964. Since then, they became one of the most used classes of antibiotics in the prevention and the treatment of orthopaedic infections.

Other classes of antibiotics that are used today in the treatment of orthopaedic infections are the amynoglicosides (gentamicin, tobramycin, amikacin), the glycopeptide antibiotics (vancomycin) and the quinolones (ciprofloxacin, ofloxacin). ❑

STAPHYLOCOCCAL INFECTIONS

Definition and classification

The staphilococs are Gram-positive bacteria, divided in 43 species and subspecies, which usually are commensal and live on skin and mucosae. Staphilococcus can be classified in coagulase-positive Staphilococcus (S. aureus) and coagulase-negative Staphilococcus (S. epidermidis, S. haemolyticus).

Pathogenesis

Studies have most frequently resulted in isolation of Staphylococcus epidermidis and Staphylococcus aureus from infected biomaterial surfaces.

Staphilococcus aureus produces a large number of enzymes (adhesines, haemolysines) and toxins. It becomes resistant to most of the antibiotics that were initially active. Almost all of the species produce beta-lactamase (1).

Staphylococcus epidermidis is frequently involved when the biomaterial surface is a polymer. Staphylococcus aureus is often the major pathogen in biometal, bone and joint and soft tissue infections. Staphylococcus aureus is the most common pathogen isolated in osteomyelitis when damaged or dead bone acts as a substratum.

The staphylococcal infections of the orthopaedic implants are a major problem of public health, because they are chronic, difficult to treat by surgical and non-surgical methods and they have a very high social cost (2).

The most frequent cause of staphylococcal infections is the perioperative contamination, and the germs come from the patient or from the operating room. There is a direct relationship between the number of persons in the operating room and the number of germs (if there are 5 persons in the operating room, the concentration of germs is over 30 times higher than in an empty operating room).

There is also a direct relationship between the presence of methicillin resistant Staphylococcus aureus (MRSA) and the length of hospitalization (2.9% for the persons outside the hospital, 44.3% for the patients that spent 48 hours in the hospital).

Ostheoarticular infections with resistant staphylococs

Ostheoarticular infections with resistant staphylococs occur in patients with infected orthopaedic implants. They require a long-duration antibiotic treatment: 3 to 4 months for infected osteosynthesis materials, 6 months for total hip arthroplasty and 9 months for total knee arthroplasty. The antibiotic treatment is an association of rifampycin and fluoroquinolones. It is the most effective antibiotic treatment (excellent bone diffusion of the antibiotics) and in some cases it leads to healing without the removal of the infected biomaterial. The administration of the antibiotics is intravenous for the first 3 weeks, and then orally. In vitro studies demonstrated that staphylococs are more sensitive to ofloxacyne than to ciprofloxacyne (3). ❏

OTHER GERMS INVOLVED IN OSTEOARTICULAR INFECTIONS

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a very resistant bacteria in external environment with a large number of virulence factors. Its natural capability of fast gaining antibiotic resistance makes it a very frequent nosocomial agent. The hospital conditions, the invasive procedures and the immunodepression of many patients creates the appropriate frame for nosocomial infection with this germ.

The ICU unit is most affected (dystrophic, immunodepressed, politrauma patients) with percentages of pseudomonas isolation up to 30%.

The multiple antibiotic resistance (even for imipenem) rises a very important challenge for the therapist in the presence of pseudomonas infection in hospitalized patients.

Klebsiella Pneumoniae

Klebsiella spp. is a group of microorganisms responsible for various infections (pulmonary, urinary, digestive, etc) with a human source being transmitted either directly (airborne particles) or through personal objects or contaminated medical instruments during invasive or non-invasive procedures. A depressed immunity (extreme ages, various diseases or nutritional status) plays a very important role in the receptivity of the infection.

There is a largely reported cephalosporine plasmid-mediated resistance due to the inappropriate use of these antibiotics that can lead to true epidemics of klebsiella infections.

Klebsiella osteomielitis, frequently a nosocomial infection, has a very poor prognosis.

Escherichia Coli

Escherichia Coli is a intestinal gram negative bacteria responsible for digestive diseases through enterotoxines and direct enteropathogenesis, the contamination occurring due to the lack of personal and institutional hygiene. Nosocomial infection with E.Coli in orthopaedic and trauma surgery is seldom, and depends mostly on the surgical discipline and on the nursing during the postoperative period, the most exposed site being the operated hip and pelvic ring.

Acinetobacter baumani

Acinetobacter baumani is an ubicuitary germ found in 25% of the population, transmitted through hands, clothing, contaminated surgical instruments, air conditioning or ventilation devices. Nosocomial infections are seldom reported in orthopaedic units, but they are quite frequent as respiratory, meningeal infections or bacteriemia in patients that need ICU admission, regardless the primary illness. The treatment usually involves cephalosporines and fluoroquinolones, but there are species that requires carbapenemes as antibiotic of choice. ❏

BIOMATERIALS AND THE RISK OF INFECTION

Pathogenesis

The two main barriers to the extended use of implanted biomaterials and complex artificial organ devices are the possibility of biomaterial-centered infection and the lack of successful tissue integration of biomaterial surfaces.

The fate of an available surface may be conceptualized as a race for the surface, a contest

between tissue cell integration and bacteria adhesion to that same surface.

Microbial adhesion and tissue integration

Microbial adhesion, aggregation, and disaggregation (dispersion) involve interactions between cells and substrata surfaces in an ambient fluid milieu. Interaction of physical and biological factors then allows bacterial attachment and adhesion. Proteinaceous adhesins (fimbriae in Gram negative bacteria), polysaccharide polymers, and surface and milieu substances interact to form an aggregate of bacteria, elemental substances, glyco-proteins, and polysaccharides in a biofilm. Additional symbiotic species may join in consortia and present as a polymicrobial infection. Characteristically, these infections do not respond to treatment until the substratum is removed (4).

Glycoproteinaceous conditioning films, derived from fluid or matrix phases containing fibronectin, fibrinogen, collagen and other proteins, almost immediately coat a biomaterial substratum and provide receptor sites for tissue adhesion.

Even in a theoretically antiadhesive system, colonization will probably be accomplished by a few pioneer bacteria that have optimal attachment abilities and use one of the several determinants of adhesion.

Biomaterial surfaces must be modified to improve compatibility and tissue integration and to resist microbial colonization in the race for the surface (5).

Stainless steel becomes infected more easily than CrCo or Ti and CrCo is infected more easily than Ti. Titanium, which is more biocompatible, is colonized by tissue cells and therefore protected from bacteria earlier than CrCo alloys. The tissue cells win the "race for the surface" more easily on titanium than on CrCo (6).

The surface of the implant

Titanium implants with a porous surface become infected with 2.5 times smaller inocula than those required for implants with a smooth surface. CrCo implants with a porous surface requires inocula 40 times smaller than those needed on smooth surfaces to become infected. In a liquid medium, germs reach the implant pores before the tissue cells, filling them quickly with colonies covered with glycocalyx.

Bacteria win "the race for the surface" more easily on porous surfaces. The multiple interstices of a porous surface facilitate the maintenance of infection and make access more difficult for antibiotics and immune system cells.

Solid intramedullary nails are more difficult to infect than hollow nails, which have a larger surface for adhesion and an interior zone which is difficult to access (7).

Bacterial adherence on biomaterials with antibiotics

Implantable materials such as PMMA, or biodegradable substances such as hydroxyapatite, calcium phosphate, polylactic and polyglycolic polymers or collagen, can be mixed with thermostable antibiotics such as gentamicin, tobramycin, vancomycin or ciprofloxacin, providing very high local concentrations, with minimal systemic toxicity. PMMA is waterproof, but the antibiotics are stored in microscopic splits and defects. Therefore, the preparation of cement by methods designed to reduce porosity (vacuum mixing, centrifugation) will reduce antibiotic release.

PMMA with gentamycin requires the inoculation of 60 times more Staphiloccocus aureus than PMMA without antibiotic to become infected (7). ❏

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis is justified at every surgical intervention involving an implant, because it reduces the rate of infection from 5% to 1%. Antibiotics can eliminate bacteria before they colonize implants or are established intracellularly in the macrophages (7).

The lowest rates of infection are obtained by the combination of intravenous antibiotics and the use of antibiotic-loaded cement.

The rates of infection are also reduced by the use of laminar-flow operating rooms and the application of simple surgical discipline.

The antibiotic prophylaxis is always indicated in immunosuppressed patients, using a second-generation cephalosporin (Cephalexin) or amoxicillin-clavulanic acid (7).

Antibiotic prophylaxis in trauma surgery

Antimicrobial prophylaxis is a necessary adjunct to the management of fractures that require surgery. In closed fractures, administration

of a first-generation cephalosporin 30 minutes before surgery provides adequate coverage (8).

It is not necessary to continue prophylaxis for more than 24 hours (9).

Antibiotic prophylaxis in open fractures

The crucial role of antibiotic administration in the management of open fractures was established in a prospective randomized study by Patzakis et al, who demonstrated a marked reduction in the infection rate when cephalothin was administrated (2.4%) compared with no antibiotic administration (13.9%) or with penicillin and streptomycin administration. The antibiotics were administrated before wound debridement (10).

The antibiotics used in the management of open fractures should be selected based on the wound microbiology.

Wound contamination with both gram-positive and gram-negative microorganisms occurs; therefore, the antimicrobial treatment should be effective against both types of germs. Currently, systematic combination therapy using a first-generation cephalosporin, which is active against gram-positive germs, and an aminoglycoside, which is active against gram-negative germs, appears to be optimal, although other combinations may also be effective. Substitutes for aminoglycosides include quinolones, aztreonam and third-generation cephalosporines (10).

Ampicillin or penicillin should be added to the antibiotic regimen when there are conditions favoring the development of anaerobic infections, such as clostridial myonecrosis (11).

The results of cultures obtained after debridement and of antibiotic-sensitivity testing may help in selecting the best agents for subsequent surgical procedures or in case of an early infection (10).

Patzakis and Wilkins reported that the combination therapy (cephalosporin + aminoglycoside) was associated with a 4.6% infection rate, whereas administration of only cephalosporin was associated with a 13% infection rate (10).

Quinolones are a promising alternative to i.v. antibiotics because they offer broad-spectrum antimicrobial coverage, are bactericidal, can be administrated orally with less frequent dosing than i.v. antibiotics and are well tolerated clinically (12).

Ciprofloxacin (like cefamandole and gentamicin) as single-agent therapy is effective in the management of type I and II open fractures (infection rates were similar).

In type II open fractures, ciprofloxacin should be used only in combination with a cephalosporin, as a substitute for an aminoglycoside (10).

Fracture type	Recommended antibiotic
Closed	First generation cephalosporin (Cefazolin, 2g i.v. loading dose, 1g i.v. every 8 hours for 3 doses)
Open type I and II	First generation cephalosporin (Ancef 2g i.v. loading dose, 1g i.v. every 8 hours for 3 doses)
Open type III	Third generation cephalosporin or first generation cephalosporin + aminoglycoside (gentamicin or tobramicin)
All open fractures	Add penicillin Add tetanus prophylaxis

TABLE 1. Choice of antibiotic therapy for closed and open fractures

Duration of therapy

Antibiotic treatment should be started as soon as possible. The duration of antibiotic administration is controversial.

Dellinger et al demonstrated that a prolonged course of 5-days antibiotic administration was not superior to a 1-day course for the prevention of fracture site infections.

Patzakis says that the duration of therapy should be limited to 3 days, with repeated 3 day administration of antibiotics at wound closure, bone grafting or any major surgical procedure (10).

Local administration

Ostermann et al demonstrated that the additional use of local aminoglycoside-impregnated polymethylmethacrylate (PMMA) beads significantly reduced the overall infection rate to 3.7%, compared with 12% when only i.v. antibiotics were used (only for the treatment of type III open fractures).

The advantages of the beadpouch technique include:
* high local concentration of antibiotics, often 10 to 20 times higher than concentration provided by systemic administration
* a low systemic concentration, which protects from the adverse effects of aminoglycosides

- a decreased need for the use of systemic aminoglycosides
- sealing of the wound from the external environment with film dressing (10). ❑

ANTIBIOTIC PROPHYLAXIS IN ORTHOPAEDIC SURGERY

Antibiotic prophylaxis in total hip arthroplasty (13)

Cefazolin 1g iv as a single dose or 1-2 doses every 8 hours, or Cefuroxime 1.5 g iv as a single dose or repeated doses every 12 hours for a total of 6g, or Vancomycin 1g iv as a single dose

Total joint replacement (other than hip) (13)

Cefazolin 1-2 g i.v. preoperative (± 2nd dose), or
Vancomycin 1 g i.v.

The antibiotic prophylaxis protocols used in the Murnau Traumatology Center, Germany (Department of Orthopaedic Surgery)

Osteosynthesis: Cefuroxime 1.5 g i.v. as a single dose in the operating room, or 3 g in obese patients.

Open fractures: first dose of Cefuroxime in the emergency room and this will be continued 3 times a day until there are no bacteriae found in the specimen taken during operation.

Arthroplasty: Cefuroxime 1.5 g as a single dose in the operating room and this is continued 3 times a day for 5 days i.v.

TREATMENT OF INFECTED IMPLANTS

Treatment must be chosen according to the type of infection, its bacteriology, glycocalyx production, antibiotic sensitivity, the general state of the patient, implant stability, bone stock and technical capabilities of the surgeon.

Antibiotic treatment in total hip arthroplasty

Treatment with antibiotics alone leads to frequent failure, except in tuberculosis, because of adherent biofilms and intracellular bacteria.

The use of antibiotics alone is indicated in supposedly aseptic exchange surgery with positive intraoperative cultures (these patients should receive intravenous antibiotics for six weeks), when exchange surgery is contraindicated in seriously ill patients, and when the surgical intervention is refused (14).

Surgical debridement along with antibiotics is indicated for acute infection with stable implants under one month from insertion and for apparently haematogenous infection. This treatment is not effective in chronic infection, because bacteria have colonized the implants and may be intracellular (15).

One-stage exchange revision arthroplasty must be associated with intravenous and local antibiotic treatment. It is contraindicated in patients with bony deficits, necrotic bone, osteomyelitis, generalized sepsis, Gram-negative, fungal, group-B streptococcal or polymicrobial infections, rheumatoid arthritis, diabetes or immunosuppression (16).

Two-stage exchange revision arthroplasty requires at least 6 weeks between the operations. The definitive prosthesis should be cemented with antibiotics (7).

Antibiotic treatment in total knee arthroplasty

In early and haematogenous infections, antibiotics alone can be used, maintaining the prosthetic components, except for the polyethylene insert (17).

In chronic infections it is necessary to replace the prosthesis with an antibiotic-loaded cement spacer (tobramycin 3.6 g + vancomycin 2 g in 40 g of PMMA) for 6 weeks, associated with intravenous antibiotic treatment, followed by the replacement of the prosthesis.(4) Some authors recommend arthrodesis because of the frequency of pain and poor function after exchange arthroplasty. The use of an intramedullary nail is the best method (18). ❑

THE ANTIBIOTHERAPY – OUR ATTITUDE

Nosocomial infections in the Orthopaedics Clinic of the Emergency Hospital "Bagdasar-Arseni" Bucharest

In a retrospective study, the incidence of nosocomial infections between 2003-2005, in our clinic, was 3.63%. The most frequent infections were the postoperative wound infections (68.59%).

The most common bacteria were: Staphylococcus (60.9%): S. aureus (35.8%), S. epidermidis (24.5%), Enterobacter (12.3%), Acinetobacter (9.6%), Escherichia coli (7.2%), Klebsiella (2.4%).

The bacteria isolated from the infection sites had the following antibiotic sensitivities:

- Staphiloccocus aureus: Amoxiclav, Ceftriaxon, Ciprofloxacin, Vancomycin
- Staphiloccocus epidermidis: Amoxiclav, Gentamycin, Ciprofloxacin, Vancomycin
- Enterobacter: Ciprofloxacin, Amikacin, Gentamycin, Amoxiclav

The antibiotic prophylaxis protocols used in the "Bagdasar-Arseni" Orthopaedics and Traumatology Clinic, Bucharest

Surgically treated closed fractures: Ceftriaxon 2g/day i.v. + Gentamycin 80 mg/day i.v., for 1 day (19).

Osteotomies, open meniscectomies, surgical interventions longer than 2 hours: Ceftriaxon 2g/day i.v. + Gentamycin 80mg/day i.v., for 1 day (19).

Type I and II open fractures: Ceftriaxon 2 g/day i.v. + Gentamycin 80mg/day i.v. + ATPA + Metronidazol 500 mg/day., for 2 days (20)

Type III open fractures: Ceftriaxon 2 g/day i.v. + Gentamycin 80mg/day i.v. + ATPA + Metronidazol 500mg/day, for 3 days (20). ❑

CONCLUSION

The antibiotics are a very important adjuvant treatment in the ostheoarticular pathology.

The antibiotic treatment cannot replace the simple surgical discipline and asepsis rules.

The antibiotics are effective in two situations: when they are used as prophylaxis and when the surgical cure is complete.

The antibiotic treatment is not effective as long as the source of infection (infected implant, bone sequestrum) is not surgically removed.

The antibiotic prophylaxis duration should be for one day. A longer duration of the antibiotic prophylaxis increases the risk of microbial resistance and the cost of the treatment.

For the antibiotic prophylaxis one can use international protocols, but our opinion is that the antibiotic prophylaxis should be made according to the specific germs of the hospital and their antibiotic sensitivity. ❑

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Address for correspondence:
Florian Purghel, "Bagdasar-Arseni" Emergency Hospital, 12 Berceni Blvd., SE 4, Bucharest, Romania, cod 041915
email address: ortopediabagdasar@yahoo.com