



Review article

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BONE INFECTIONS AND ANTIBIOTICS USE IN ORTHOPAEDICS

SUMMARY

Bone infections are always a burning issue in orthopedic surgery. The treatment of bone infections is very complex, long-lasting, persistent and expensive, often followed by permanent invalidity. Modern approach to treatment of bone infections is based on surgical interventions, use of antibiotics, immunologic treatment and rehabilitation. The significance of the antibiotics is great in therapy and prophylaxis of bone infections. Antibiotic therapy is used taking into account the causes of the illness and its sensitivity to certain antibiotic. The most common cause of bone infection is *Staphylococcus aureus*. The choice of antibiotic therapy can be made concerning several important factors: age of the patient, chronic diseases, type of the injury, the period of time between the injury and hospitalization, the duration of the operation, surgical technique used, operation room. Only the unity of surgical, antibiotic, immunologic and physical therapy can provide efficient management of bone infections.

Key words: bone infection, antibiotics

INTRODUCTION

Antibiotics have a key role in the prevention and treatment of skeletal-joint infections, though only the unity of surgical, antibiotic, immunologic and physical treatments warrants success. The significance of antibiotics has been pointed out in the prophylaxis of bone infections, although its use cannot cover the maltreatment in operative work (1). Even though bone infections have been known since the earliest history of human civilization, nowadays they are still a burning problem in modern orthopedics and traumatology. Postoperative bone infection is the most difficult complication after the operative treatment in orthopedics and traumatology. It requires long-lasting, expensive treatment and it is often followed by permanent invalidity. The duration of treatment, the recidivism, various number of operations, socio-psychological consequences for the

patient and his surroundings, as well as the fear of potential amputation throw a special light on this problem. Highly active modern way of life and numerous daily activities are creating the possibilities for injuries which require surgical treatment which could lead to various complications, such as infections. Bone infections are still a burning orthopedic and traumatologic problem. Besides the dynamics of the existence and the rate of occurrence in structuring general and specific morbidity and mortality, the socio-medical and epidemiological significance of infections can influence the quality of life, including health, psychological, economical and social consequences, as well as various sensitive interactions between the patient and his/her surroundings (2). Bone infections require long-lasting, persistent and expensive treatment. These infections can often cause disability. The knowledge of all aspects of this illness can provide careful preparations and imple-

mentation of both preventive and treatment measures. The importance of surgical microbiology grew since Pasteur and Lister, and lately in Altemeier's work it became the subject of various surgical research and interests. Nowadays we have numerous researches in surgical microbiology which are based on the prevention treatment of post-operative infections with antibiotics in correlation with general status of the patient and creation of high-risk-factors concerning unspecific infections in post-traumatic period. The factors of high risk for the onset and development of infections related to the patient are: sex and age, overweight, nutritive status, hypovitaminoses, chronic illness, infections, corticosteroid and immunosuppressive therapy. In infection prevention it is necessary to pay attention to the monitoring of the patient, operation rooms must fulfill the high criteria of asepsis and antisepsis, the qualification of the surgical staff, appropriate surgical techniques (as much as possible atraumatic, without contamination, hematoma progression), the duration of the operative procedure, postoperative care of the patient, appropriate use of antibiotics in prophylaxis (3). The base for successful treatment of infection is the injury and fast diagnostics. Osteomyelitis or osteitis both denote bone tissue infection. Friedrich was the first who used the term "osteitis" in order to make the term "osteomyelitis" reserved for hematogenic processes. For every specific patient there are several factors that influence the nascent stage and the development of osteomyelitis such as: patient's immune system, virulence and bacteria type, type of bone-break, operation room, operation staff, operative technique, size and duration of the operation. The expected percentage of the infections after pure orthopedic surgeries cannot be over 1%. As for the infection causes, in 70% of the cases patients are under *Staphylococcus aureus*. In other cases we are dealing with gram-negative bacteria. The bone infections are long-lasting and one can never be absolutely sure that the process totally resolved. Every immune deficiency as the consequence of some other disease could provoke the process in skeletal system. Stanković at al. have stated that in 320 cases of post-traumatic osteomyelitis recidivism is possible in 74,3% of the cases, sometimes even after 20–30 years of uninterrupted asymptomatic period (4).

HISTORICAL DEVELOPEMENT OF UNSPECIFIC BONE INFECTION TREATMENT

The first description of the open fracture infection was found on Smith's paper, dating from the period 5000–3000 b.c. Even the ancient Egyptians

used the term "the pus secretion" from the bone cavity. The treatment was based on immobilization with wooden cortex crimped by flaxen bandages and by setting up the bandages out of herbal and animal extracts to the injury. In ancient China, one used to burn the injured part of the body with different herbs and wooden chops. These kinds of burns would provoke the appropriate inflammable reaction that would "hunt for the infection". Dupuytren was also one of the followers of this method. Hypocrates (3–2 century b.c.) thought that the bone infection can be treated only with immobilization and relaxation. The surgeons in ancient Rome, Celsus and Antyllus (1 century b.c.) have very precisely described the way of sequestrectomy and excision of the necrotic bones using the hot iron strap. Teodoric, 1266 has suggested the wine bandages, and De Mondeville, 1260–1320, used to make the ablution with boiled water after the mechanical cleaning of the injury. The ablution system "drop by drop" which is the basis of the modern washing technique (according to the work of Papineau) was used in XIII century. In XIV century, french military surgeon Pare and german surgeon Schultetus insisted on ablution of osteomyelitical seat by removing the ill bone. In Lancet magazine, Lister in 1867. wrote an article "About new method of treating multiple fractures, abscesses and similar injures" which wrote a new page in medical history. Two years later, Pasteur developed the pathogenic influence of bacteria, which started a new era in the development of medicine, especially surgery. Mikulicz and Halsted have earned a great credit and respect in treatment of post-operative infections: Mikulicz (1880) established the use of sterile gloves made of white cloth, and Halsted (1890) was the first who used the sterile gloves made of thin rubber. In 1928. Fleming discovered the penicillin, starting the new era in infection treatment. Jensen (1939) discovered the infection frequency decrease from 27% to 5% by using the sulphonamye for cleansing and washing open fractures (4).

CLINICAL IMAGE AND DIAGNOSTICS OF THE UNSPECIFIC BONE INFECTION

The bone infection in early stage can be seen 3–10 days after the operation, open fracture or sterile injury. All common symptoms of inflammation are present. The skin near the injury is red, followed by pus secretion (figure 1). Increase of body temperature, fever and exhaustion are some of the symptoms of the infection and they are result of the slight bacterial septicemia. The infection cannot exist with the absence of the bacteria, but not every bacteria cause the infection. Various factors can determine



Figure 1. Chronic bone infection after the osteosynthesis of distal part of femur

the intensity of the infection. Early operation, radical debridement of the injury, stabilization of the fracture, early reconstruction of the soft tissue coverlet, in-time use of appropriate antibiotics and good post-operative care can decrease the possibility of infection. Kahn and Pritzker (1973) consider that the existence of the bacterial bone infection could be easier to get if the fracture is also combined with great damage of the periost, bones or bone marrow, which together with vascular occlusions isolate this area from body's protective mechanisms and the influence of the antibiotics. Late unspecific bone infection has every common symptoms of the inflammation but it can also be seen that it occurs several months or even a year after the operation. With hidden infections caused several months or a year after operation, the most common isolated bacterial cause is *Staphylococcus aureus*. It is described with lack of common inflammation symptoms, existing pain in operated area, permanently increased sedimentation and radiographically visible osteolysis near the implantation. The infection after longer asymptomatic period is the result of contamination of operated injury with smaller number of virulent bacteria (Graunan, 1993), when the body was defensive enough to fight the infection so it couldn't be manifested. Later in life when the immunity decreases as a result of an injury or some illness, the bacteria are active and clinically manifested infection can be seen. The second possibility is hematogenous dissemination from some other focus in the body (gastrointestinal, genitourinary, respiratory etc.)(4).

Many lab tests, conventional radiograph methods, CT, MRI, scintigraphy and biopsy of the seat can be used to detect bone infection with different stage of sensitivity and specificity. The lab examinations necessary for the diagnostic are chematological and bacteriological.

Erythrocyte sedimentation (SE) is one of the most common examinations. Its value is based on

blood albumen and their internal correlations (the relations between albumin and globulin), sacrificial blood expansion, ion concentration, volume percentage of blood cells, size and the shape of the erythrocytes and the number of lipids in blood. Because of its availability and simplicity this routine lab examination method is very important in bone infection diagnostics, because the increase over 20 during the first hour can show the infection process whose intensity can be determined by some other methods.

Alkaline phosphatase is emitted by the osteoblasts and its increase can show their activity. Normal values of alkaline phosphatase are 24–28 IU/ml for adults and 35–155 IU/ml for children.

The plasmatic proteins, located in blood from 6,2- 8,8 g%/l can be classified according to their chemical characteristics on albumin, globulin and fibrinogen.

Albumins are by quantity the largest fraction of the proteins (52-65%) and their role is very important for preservation of the plasma osmotic pressure and for transportation of various useful and harmful plasma constituents. Their synthesis occurs in the liver. Hard infections can produce faster antibodies and decrease of the albumin value, for remaining the colloidoosmosis pressure.

Globulin, which makes 35%–45% of all protein serums, is synthesized in reticuloendotelial system. Their most important role in the body is to defend the body from the infection, since these fraction contains antibodies (IgM, IgA, IgG)(5).

C reactive protein (CRP). Tillet and Francis (1930) have noticed that the serum of patients suffering from the acute pneumonia, rheumatic fever, bacterial myocarditis, staphylococcus infections and some other infective conditions, can produce precipitation together with somatic C-polysaccharide pneumococcus with the existence of calcium ions. Losfstrom (1941.) have developed one serum component which combined with calcium ions result with capsular swelling pneumococcus and it is known as "Non-specific Capsular Swelling Substance" identical to the substance which causes precipitation and it is called C-reactive protein, CRP-protein of acute phase ("Acute-Phase-Protein"). CRP is synthesized in periportal liver cells and the primary sign for its synthesis is interleukin-1, which creates macrophage where the tissue is damaged. Sudden increase in early phases of inflammatory process can suggest that one of its roles is to begin the system complement activation as for the first line of body defense. It can be shown in serum 1–4 hours since the beginning of the acute phases and its maximum is after 8 hours (6–8). The decrease of the value means that the inflammatory process is resolved, but, as Bašćarević (1992) pointed out, it can not be determined for sure (9,10).

Bacteriological examination is a special kind of lab work with main aim to find out what bacteria is the cause of bone infection. The *Staphylococcus pyogenes aureus* was discovered by Pasteur (1880) in a pus culture from the osteomyelitic seat. Blood, pus from the abscess bone cavities, fistulae cavity, sequester and from the surface of the injury is the material suitable for the isolation of the cause of the infection. The existence of bacteria can be proved with seeding the taken material on the appropriate basis. In the same time one can determine the sensitivity of the bacteria to antibiotics (antibiogram), which is really important for the influence of certain antibiotics (11).

Pathohistologic examination can result in minimizing differential diagnostic dilemma, especially in separating specific from unspecific bone infections. Malignant processes in the bones are often difficult to differentiate from ordinary osteomyelitis, so the pathologic examination is the best diagnostic method.

Radiographic examination can make morphological changes provoked by bacteria on the bones visible. Standard radiograph of the locomotive system can be x-rayed in two projections. For objectivity in rating the bone stage it is important to compare the x-rays with the ones made previously. The first morphological changes visible on the x-ray can be seen after 15 to 21 days since the beginning of the illness, because it takes some time to affect the periosteum and for osteoblasts to start forming new bones. After every x-ray in chronic osteomyelitis the presence of bone condensation, periosteal reaction, osteolysis as one of the common signs of bone destruction, the presence of the sequestrae as a part of the rejected necrotic bone must be analyzed. After cured bone infection, the bone remains permanently deformed with changed structure (figure 2).

Fistulography, contrast conventional radiography method, placing the contrast fluid in fistulae



Figure 2.
X-ray
of chronic osteitis
of femur

cavity one get precise view of the length, shape and position of fistula cavity, what makes the operation easier.

Computer tomography (CT) is used to diagnose bone infection especially in the area when standard radiography can not discover philligran changes because of their complexity. It can be used in skeletal-spinal processes in the pelvis area.

The magnetic resonance image (MRI) is a modern diagnostic method with wide indication of use (12). Contraindications for MRI examination are: steel implants with ferromagnetic characteristics, pace-maker implants and insulin pump, patents with cardiorespiratoric supplies. Patients with implants made of high-quality mixtures (titanium, vanadium) can be examined, but it is necessary to have the manufacturers' guide with exact structural components of the implants.

TREATMENT OF UNSPECIFIC BONE INFECTION

Numerous operative techniques and optional methods in treating bone infections have pointed out that the treatment plan must be appropriately made for every individual patient. Modern way of treatment can be classified into 4 (four) groups:

SURGICAL TREATMENT

- Radical debridment of the infection seat
- Fragments' stabilization
- Bio-stimulation and filling the bone defects
- The skin
- Amputation

ANTIBIOTIC TREATMENT

- Systematic antibiotic therapy
- Local antibiotic therapy

IMMUNOLOGY TREATMENT

- Transfusion of the fresh blood
- Receiving gamma-globulin

REHABILITATION

- Chinesytherapy
- Heliotherapy and balneotherapy
- Working therapy
- Socio-psychological support

Radical debridment means the removal of all avascular necrotic tissues, bones and nearby soft-tissue-structures until it provokes bleeding from the nearby tissues, as well as detailed washing with aseptic solutions, hydrogen peroxide or povidon-iodid. It is important to take the injury culture for biogram and anti-biogram results during the injury control or after the operation.

The next procedure which is a part of the modern treatment protocol of open fractures is stabilization of the fracture with external fixation (Gustilo

1982) (13). Fluxing drainage can be set up after the radical debridment for mechanical washing of osteomyelitic seat. Sterile physiological solution can be used 6000 ml per day without any antibiotics, although some authors are insisting on the significance of local influence of antibiotics. Cemently beads combined with antibiotics can be used for filling the bone cavity after debridment osteomyelitic seat. Hyperbaric oxygen can help in treating bone infection in order to make better oxygenization in cases of bad-blooded-tissue, inhibit the grow of microorganisms; increase the capillarity in the seat of the infection and to improve the influence of antibiotics.

– The goal of blood transfusion is to increase the number of defensive units for patients with bone infection and to improve detoxication of the body until the metabolic products fall apart as well as their toxins. Gamma globulin is protein fraction of plasma, which contain anti-bodies taken out from the blood of different blood donors. It can be supposed that all donors were exposed to bacteria and viruses, so they have created certain antibodies which can be taken out from the blood serum and used in treating patents in need.

– Normalization of the locomotive function for patients with bone infection is the main aim of the treatment. The patient can safely return to his/her working place, or be transferred to some other which won't jeopardize the existing illness. That is not just the task for orthopedics, but also for physiatrists, social worker and psychologist. Their cooperation can warrant the successful treatment and recovery of the patient.

ANTIBIOTIC TREATMENT

The blood clot in the cavity made after debridment of the osteomyelitic seat is a good base for growing and development of bacteria. Willson et al (1971) have concluded after the experiment that the concretization of the antibiotic given parenterally preoperationally for a longer period is in increase in hematoma rather than in circulating blood (14). The cycle of antibiotics between the blood system and the hematoma is based on the mechanism of passive diffusion and it is minimal. Use of antibiotics after the operation in orthopedics can not provide sufficient concentration of antibiotic in hematoma. Speaking of antibiotics use in orthopedics, it is necessary to prevent bone infections and the use of antibiotics in treating bone infections (15, 16). In cases of open fractures the choice of antibiotics is at first purely empirical, but after the results of bacterial culture analysis, therapy can be changed according to the results of anti-biogram (17). Dickey

et all. (1989) are recommending the use of 1g Cephazoline/every 8 hours during first 72 hours since the injury appears for preventing the bone infections on open fractures (18). Patzakis et all. (1974) recommend early use of Cephalothin in preventing infection. They had 2,3% of infections after the operative treatment of open fractures when using Cephalothin for treatment (19). One group was using the Penicillin and their percentage of infection was 9,7%. The control group had the highest rate of infections-13,9%. This control group has not been treated with antibiotics for prevention. Gustilo (1987) recommends for open fractures of 1st and 2nd stage use of 1g Cephazoline/every 8 hours in duration of 3 days. For open fractures of 3rd stage he recommends the use of 1g Cephazoline/every 8 hours and Genthamycine 2mg/kg in duration of 5 days (11). Some authors also include here Penicillin-4 000 000 units every 6 hours because of the possible existence of anaerobic bacteria. Extensive use of antibiotics for 3rd stage of open fractures is caused by the fact that the cause of the infection are usually Gram negative bacteria, and not so rarely even mixed bacteria (figure 3). Tengve et all. (1978) had 1,8% of infections after osteosynthesis of a broken hip in patients receiving antibiotic prophylaxis, while the percentage of the infections among the patients without post-operational antibiotic treatment was 16,9%. For prevention was used Cephalothin 2g pre-operative and two days more after the operation (20). Dulić (1994) suggested the use of Cephtriaxon in



Figure 3. Bone infection of distal tibia after open fracture (IIC stage by Gustile).

preventing bone infections in hip surgery-2 hours before the operation, 1g during the operation and 2g daily during next 3 days. It is generally accepted that prevention, especially in hip surgery, must be made before the operation and 72 hours after the operation (21, 22). In cases of reduction of open fractures with internal fixation it is recommended for prevention the use of one dose of Cephtriaxon-2g during the operation. Bodky et all. (1993) are recommending 2 doses of Cephalosporine in preventing the infection after internal fixation of broken hip (23).

Speaking of antibiotics use in infection treatment, therapy can be devised according to the biogas or anti-biogram. Table 1. and figure 4. are presenting the most often causes of skeletal-joint infections on Orthopedic and Traumatology Clinic in Niš for period from 1993-2001. Figure 5. presents the sensitivity and resistance of some antibiotics for Staphylococcus aureus, which was the most often the cause of infection for period from January 1st-March 1st 2004. Out of 68 positive bacteriologic cultures, Staphylococcus aureus has been isolated in 33,82% of all cases.

CONCLUSION

Bone infection is always a burning problem in orthopedics and traumatology and it requires

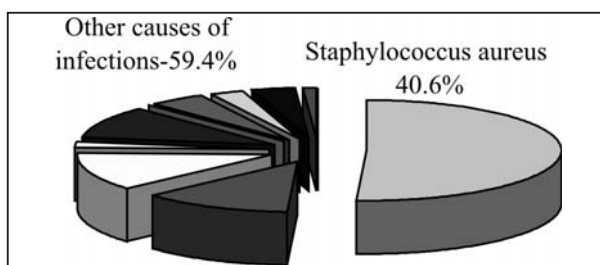


Figure 4. The percentage of staph. Aureus and other causes of the infections

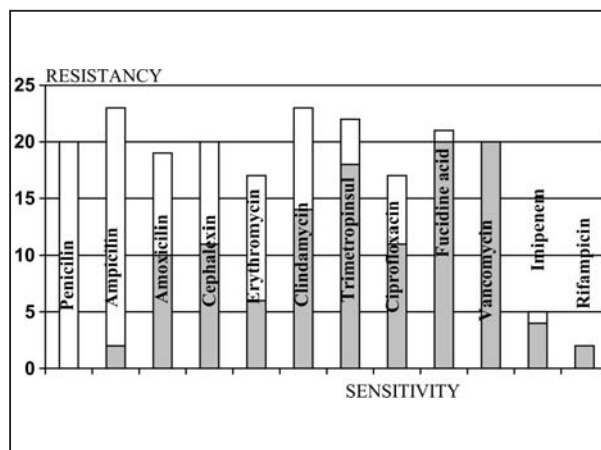


Figure 5. Sensitivity and resistancy of the Staphylococcus aureus on certain types of antibiotics (Institute for health protection - Niš)

Table 1. Most often isolated causal agents from the injury culture on the Orthopedic and Traumatology Clinics in Niš, from year 1993–2001.

THE CAUSE	1993	1994	1995	1996	1997	1998	1999	2000	2001	TOTAL	%
Staph. aureus	43	35	47	26	50	44	33	27	38	346	40.6
Staph. epidermidis	8	4	4	1	11	12	10	10	8	91	10.6
Pseud. aeruginosa	2	6	9	8	20	13	16	9	10	84	9.8
Accinetobacter sp.	8	9	10	6	8	8	23	9	-	14	1.6
Enterobacter spp.	9	2	8	7	9	3	10	3	18	69	8.1
Esch. coli	5	3	7	3	3	-	10	1	9	129	15.1
Citrobacter spp.	7	-	2	3	5	3	5	2	6	38	4.4
Str. haemolyticus	3	5	1	-	1	3	4	2	6	33	3.8
Proteus mirabilis	2	-	2	4	-	3	2	2	4	20	2.3
Klebsiella spp.	3	4	4	-	-	1	1	1	2	24	2.8
Proteus vulgaris	1	-	3	-	-	-	-	3	-	7	0.8
Serratia sp.	-	-	-	-	-	-	-	-	1	1	0.1
TOTAL	91	68	97	58	110	90	114	69	101	852	100

long-lasting, expensive and persistent treatment. The use of antibiotics in treating bone infections is very significant, but the role of antibiotics should not be over-emphasized. We can not ignore some important factors such as: age and chronic illnesses, type of the injury, the time between the injury and

the hospitalization, duration of the operation, operation technique, operation room, and postoperative care. Only the unity of surgical, antibiotic, immunology and physical therapy give us hope for the efficient treatment of bone infections.

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KOŠTANE INFEKCIJE I UPOTREBA ANTIBIOTIKA U ORTOPEDIJI

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SAŽETAK

Koštane infekcije su uvek aktuelni problem ortopedске hirurgije. Lečenje koštanih infekcija je složeno, dugotrajno, uporno i skupo, često praćeno trajnim invaliditetom. Savremeni pristup lećenja koštanih infekcija podrazumeva hiruršku intervenciju, upotrebu antibiotika, imunološko lećenje i rehabilitaciju. Značaj antibiotika je važan u terapiji i profilaksi koštanih infekcija. Antibiotiska terapija se primenjuje u zavisnosti od uzročnika i njegove osetljivosti na određeni antibiotik. Najčešći uzročnik koštanih infekcija je *Staphylococcus aureus*. Važni faktori u izboru antibiotiske terapije u ortopediji su: starost bolesnika, hronične bolesti, vrsta povrede, vreme proteklo od povrede do hospitalizacije, dužina operacije, operativna tehnika, operaciona sala. Samo jedinstvo hirurškog, antibiotskog, imunološkog i fizikalnog lećenja omogućava efikasno lećenje koštanih infekcija.

Ključne reči: koštana infekcija, antibiotici