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Review

Microbiological Aspects of Joint and Bone Infections

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Abstract

Bone and joint infections can be critical and life-threatening conditions due to the numerous complications they can elicit and provoke in the human organism. Orthopaedic infection can be either acquired during or after a normal surgical procedure, or a complication triggered by previous operations. The aim of this study was to investigate the microbiological aspects of joints and bone infections, the diagnostic methods for their detection and the way of treating. There are numerous etiological agents that cause post-surgical infections in orthopaedics, mainly bacteria, with the predominant role of Staphylococcus aureus. Infections may occur in both natural and artificial joints. However, people with artificial joints are more susceptible to such type of infection. Microbiological investigations are needed to confirm the final diagnosis. Early appropriate choice of parenteral antimicrobial agents may reduce the risk of complications, especially in comorbid patients.

Keywords: orthopaedic infections, microbiology, diagnostics

Резюме

Костните и ставни инфекции могат да бъдат критични и животозастрашаващи състояния поради многобройните усложнения, които могат да изострят и провокират в човешкия организъм. Този тип инфекции могат да възникнат по време или след обикновена хирургична процедура, както и да бъдат отключени вследствие на предишни оперативни намеси. Целта на настоящото проучване бе да се проучат микробиологичните аспекти на ставните и костни инфекции, диагностичните методи за детекцията им, както и възможните терапевтични опции. Голям брой микроорганизми се асоциират с пост-хирургични инфекции в ортопедията като това са основно бактерии с предоминиращ представител Staphylococcus aureus. Засягат се, както естествените, така и изкуствените ставни повърхности, като пациентите с изкуствени стави са по-предразположени към инфекции. Микробиологичното изследване е необходимо за потвърждаване на окончателната диагноза. Навременно адекватно парентерално антимикробно лечение може да намали риска от усложнения особено при коморбидни пациенти.

Introduction

Orthopaedic infections are considered to be a serious condition. They are associated with prolonged morbidity and disability and can induce patients' death if left untreated (Colston and Atkins, 2018). In most of the cases these types of infections are acquired in the operating field, following arthroscopy, or as complications after bone surgery (Zekry *et al*., 2019). Statistics have shown that up to 20% of the patients who did undergo intra-abdominal procedures developed bone infections as post-operative complications and up to 2-5% of such complications occurred in patients after extra-abdominal operations. Many etiological factors are associated with the development of post-surgical infections in orthopaedics, mainly bacteria, with

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the predominant role of *Staphylococcus aureus* and less commonly viruses, fungi and anaerobic bacteria (Mathew and Ravindran, 2014; ter Boo *et al*., 2015; Combs and Cox, 2018). All patients can be affected, especially patients with comorbidities and children, due to the low activity of their immune systems (Colston and Atkins, 2018). The most common types are osteomyelitis, prosthetic joint infection, and arthritis. These infections can cause several complications, including delayed vascular malformations, sepsis, multiple organ dysfunction syndrome (MODS) and even bone necrosis (Zekry *et al*., 2019). The clinical presentation includes pain, fever and swelling. The diagnosis is based on the clinical symptoms and the microbiological investigation results. The antimicrobial therapy is concerted according to patients' age, the presence of any concomitant diseases, the severity and stage of the infection (Kaplan, 2014).

Microbiological aspects of septic arthritis

Septic arthritis, or infectious arthritis, is a pyogenic infection, usually considered to be one of the main serious and challenging infections in orthopaedics and highly associated with increased rate of mortality. Other terms used to describe this type of infection are: suppurative arthritis, purulent arthritis, pyoarthritis, and "Tom Smith arthritis" in infants (Nade, 1977). Septic arthritis is a joint infection, acquired mainly after surgery of the musculoskeletal system (Shirtliff and LeFrock, 2003). The disease may affect all ages and all types of bones and joints. Infections can occur in both natural and artificial joints. People with artificial joints are at higher risk than the general population. The persistence of infection remains a very common cause of failure of shoulder, hip and knee arthroplasty (Colston and Atkins, 2018). Diagnosis of septic arthritis usually encompasses the clinical presentation, the symptoms reported by the patients such as joint pain, fever, lack of motility, and the microbiological investigations used to establish the final diagnosis. Early antibiotic treatment should be prescribed immediately. Timely therapy reduces the chance of the infection progressing to an irreversible stage. Patients who fail to achieve full recovery with antimicrobial therapy only require subsequent surgical procedures (Colston and Atkins, 2018).

Aetiology

Septic arthritis is a polyetiological infection. The variety of etiological agents involved in infectious arthritis are listed in Table 1.

Table 1. Types of septic arthritis according to the causative agent and source of infection

Type of arthritis	Causative agent	Source of infection
Bacterial septic arthritis	*S. aureus*	Trauma, skin infection, ear infection
	Beta-haemolytic streptococci	Bacteraemia
	Escherichia coli	Gastro-intestinal infection and urinary tract infection
	Neisseria gonorrhoeae	Sexually transmitted in adults, through placenta in neonates
	Haemophilus influenzae	Direct invasion
	Propionibacterium acnes	Shoulder arthroplasty, post traumatic surgery
	Salmonella species	Direct invasion in children
	Shigella species	Enteric infection
	Brucella species	Infected animals
	Chlamydia species	Sexually transmitted infection
	Yersinia species	Lined with HLA-B2 antigen, Reiter's syndrome
Viral septic arthritis	Hepatitis B virus	Viraemia
	Rubella virus	
	Parvoviruses	
	Alphaviruses	
	Mumps virus	
Mycotic septic arthritis	*Candida albicans*	Haematogenous dissemination
	Sporothrix schchencii	
	Coccidioides immitis	

These pathogens have the ability to invade any joint cavity and to provoke various symptomatic clinical presentations (DiStefano and Pinney, 2010; Kaplan, 2014). As regards the causative agent, septic arthritis is mainly classified into three groups: bacterial, viral and fungal septic arthritis (Mathew and Ravindran, 2014). *S. aureus* is considered to be the main microbial factor in bacterial septic arthritis. The source of *S. aureus* could be either skin infection, ear- or meningeal infection. Other agents include: beta-haemolytic streptococci, especially in diabetic patients and patients with ulcers, *Salmonella* in children, *N. gonorrhoeae* in neonates and in young sexually active adults, *Brucella* species in patients exposed to infected animals or milk products, and *Mycobacterium tuberculosis* in patients with lung diseases (Gaston and Lillicrap, 2003; Mathew and Ravindran, 2014). Gram negative bacteria as *E. coli* are also associated with this type of infection (Lin *et al*., 2017). Less commonly, anaerobic microorganisms have been identified as a cause in the development of this type of arthritis, namely *P. acnes*, which colonizes the sebaceous follicles in the skin of the upper body (Kadler *et al*.,2015). Viruses, such as Hepatitis B, Epstein-Bar, Alpha- and Parvoviruses, are able to affect all joints by the deposition of immune complexes on the bone articulations (Marks and Marks, 2016). As etiological agents of mycotic arthritis, *S. schencii*, *C. immitis* and *C. albicans* are usually listed (Kemper and Deresinski, 2014).

Risk factors

Septic arthritis affects all ages. Elderly patients and children are more predisposed. However, age is not considered to be the only risk factor that plays a major role in the evolution of the disease. Many other risk factors have been highly linked with the invasion, spread and expansion of the infection such as: immunodeficiency or immune disorders (patients with HIV, autoimmune diseases, etc.), drug abusers, previous surgical procedures, patients with catheters, presence of concomitant diseases (such as diabetes mellitus), overuse of intra-articular corticosteroids, traumas (ter Boo *et al*., 2015; Combs and Cox, 2018). Additionally, social factors, such as low social economic status and poor hygiene play a significant role in the aetiology of septic arthritis (Smith *et al*., 2006; Colston and Atkins, 2018).

Pathogenesis

The disease occurs mainly through direct inoculation of the microbial agent into the blood stream (Mathew and Ravindran, 2014). Different types of arthritis have different routes of infection. In bacterial septic arthritis, the routes of infection include haematogenous spread from a focus elsewhere in the body, such as meningitis or cellulitis, or from neighbouring soft tissue infections; direct penetration due to traumas after surgery or joint puncture, insertion of instrumental catheters used in urology and cardiology, prolonged tourniquet time. Immune-mediated mechanisms are also involved - patients with HLA-B27 antigen are predisposed to *Salmonella* arthritis (Gaston and Lillicrap, 2003). Viral and fungal arthritis are usually due to haematogenous dissemination (Smith *et al*., 2006).

Diagnosis

Early diagnosis of arthritis is the key to successful treatment and faster recovery. The diagnosis is based on the patient's history, the clinical examination and the microbiological investigations. Clinical symptoms usually present as pain, swelling, loss of motion, and fever (Mathew and Ravindran, 2014; Moro-Lago *et al*., 2017). Microbiological investigations include cultural and non-cultural techniques. Examination of synovial cultures are useful, especially in the diagnosis of anaerobic arthritis. Increased number of polymorphonuclear leukocytes, changed levels of protein and glucose are usually detected. Tissue culturing is more sensitive than synovial culture in detecting fungal infections. Microscopic examination could reveal tuberculosis granuloma related to arthritic infection. Prosthetic component investigation is necessary (Smith *et al*., 2006). The non-cultural techniques involve common blood tests, immune essays, nucleic acid amplification test, confocal and electron microscopy. Common blood tests usually reveal increased level of inflammatory biomarkers (CRP and ESR), neutrophilia and leucocytosis. High levels of specific IgM and IgG are found in *Salmonella*-associated arthritic infection (Gaston and Lillicrap, 2003). HLA typing is an option for these patients. ELISA tests detect increased levels of IFN-γ in patients with *C. albicans* arthritis. PCR of biological specimen is the most precise method for detection of microbial pathogens. Imaging methods (MRI, CT scan, ultrasound) are used to confirm septic joint infection by the presence of effusion and tissue changes (Nade, 1977; Mathew and Ravindran, 2014).

Antibiotic treatment

Antimicrobial treatment in orthopaedic infections should be provided as soon as the final diagnosis is made to lower the rate of early complications, to protect the implanted joints and as a prevention of bacteraemia. There is controversy in

the literature regarding the choice of antibiotics and the duration of prophylaxis. The treatment depends mainly on the causative agent, the age of the patient, the presence of any risk factors and the stage of the infection. The administration of antibiotics in septic arthritis is mainly through the intravenous route. Vancomycin has shown high efficacy against Gram positive bacteria such as staphylococci, including MRSA (Methicillin resistant *S. aureus*) and streptococci (ter Boo *et al*., 2015). In neonates, Cefotaxime and Benzylpenicillin are given as empiric therapy. In infants from 6 months to 2 years Ceftriaxone is the drug of choice and in patients above 2 years Cloxacillin is administrated. In case of *S. aureus* infection, cefotaxime is usually applied. In children aged 3 years and above, 3rd generation cephalosporin is the drug of choice. The treatment period varies between 10 and 14 days (Buxton and Moran, 2003; ter Boo *et al*., 2015). Some specialists recommend corticosteroids as adjuvant therapy with antibiotics, especially in children with septic arthritis, since it has shown to shorten the days spent in hospitals (Qin *et al*., 2018). In adults, the primary therapy is 3rd generation cephalosporins. They can be used alone or in combination with Oxacillin or Vancomycin (Frank and Tacconelli, 2012). In patients with MRSA infections, Vancomycin is considered to be the antibiotic of choice, Linezolid can be also effective as well as Teicoplanin alone or in combination with Ciprofloxacin (Schildgen, 2018). In patients infected with sensitive *S. aureus*, Cefuroxime, a 2nd generation of cephalosporin, is administrated (Iqbal *et al*., 2017; Combs and Cox, 2018). Rifampicin is the drug of choice in mycobacterial, while Clindamycin in anaerobic arthritis. Antifungal therapy, such as Amphotericin B or Itraconazole, are administrated in fungal septic arthritis. Other options include Ketoconazole and Fluconazole. Surgical debridement along with antifungal antibiotics is highly recommended due to the fact that it helps in the faster eradication of the infection (Smith *et al*., 2006). In gonococcal infection, Penicillin G is the first-line therapy, third-line generation of cephalosporin, such as Ceftriaxone or Ceftizoxime can be also administrated (Molyneux *et al*., 1998). For deep *P. acnes* infections, Vancomycin and Clindamycin are the first-linetherpy, however 1st generation cephalosporin and penicillins can be effective, too. The prophylaxis in adults should proceed up to the 3rd week, while in patients with infections due to prosthetic materials it should continue until the 6th week. Surgical procedure as arthrotomy should be taken under consideration if the treatment with antibiotics is inefficient (Shirtliff and LeFrock, 2003; Buxton and Moran, 2003; Schildgen, 2018).

Microbiological aspects of osteomyelitis

Osteomyelitis, according to Waldvogel classification, is an acute or chronic bone infection with/or without bone marrow involvement. This type of disease is more common in children than in adults, although some patients over the age of 40 are more susceptible to infection. Osteomyelitis is considered to be a polymicrobial infection. Several microorganisms are associated, including *S. aureus*, group A streptococci, *H. influenzae* (Sia and Berbari, 2006; Lima *et al*., 2014). Unhealed fractures are considered a risk factor. The infection develops after haematogenous dissemination or direct inoculation of the pathogen into the blood stream. Osteomyelitis usually presents with general and nonspecific clinical symptoms, such as pain, fever, swelling and tenderness. However, the clinical presentation is not always sufficient for a definitive diagnosis. Microbiological investigations supported by imaging methods are required. Imaging methods alone are not preferred for early diagnosis, as no changes can be detected into the bone tissue. Treatment includes antimicrobial therapy followed by surgery when antibiotic therapy fails to achieve complete healing. Delay of treatment could lead to malignant transformation (ter Boo *et al*., 2015).

Aetiology

Osteomyelitis is caused by several pathogens from different groups of bacteria, fungi and viruses. The most common bacterial microorganism is *S. aureus*, which affects all ages. Other bacterial pathogens associated with osteomyelitis include: *E. coli* and other Gram negative rods, group A and B streptococci, *N. gonorrhoeae*. In newborns, less than 4 months old, the most common causative agents of osteomyelitis are: *S. aureus*, group A and B streptococci. In patients from 4 months up to 4 years *S. aureus*, H. infleunzae and Enterobacter species are reported (Offiah, 2006). In adult patients, *S. aureus* and occasionally *Salmonella* serotypes are found additionally to *N. gonorrhoeae* in sexually active adults. Patients with sickle cell anaemia are more susceptible to osteomyelitis caused by *Salmonella*. *C. albicans* and Hepatitis B virus are the most common causative agents of fungal and viral osteomyelitis, respectively (Colston and Atkins, 2018; Lima *et al*., 2014; Sia and Berbari, 2006). The causative agents of osteomyelitis by age are summarized in Table 2.

Table 2. Causative agents of osteomyelitis according to the age group

Age group affected by osteomyelitis	Most common aetiological pathogens
Newborns (<4 months)	*S. aureus, Enterobacter spp., group A* and *B Streptococcus*
Children (4 months - 4 years)	*S. aureus, group A streptococcus, H. influenzae, Enterobacter spp.*
Children, adolescents (4 years - adult)	*S. aureus (80%), group A Streptococcus, H. influenzae, Enterobacter spp.*
Adult	*S. aureus,* occasionally *Enterobacter* or *Streptococcus*

Risk factors

The disease can occur as a complication of previous operations and traumatic injuries, or after a joint transplantation. Immunocompromised patients, drug abusers, prolonged treatment with corticosteroids, presence of malignancies and poor hygiene can be added to the list of risk factors (Colston and Atkins, 2018).

Pathogenesis

Osteomyelitis is an infection caused by haematogenous spread of the microorganism. Long bones are mainly affected as well as the vertebra. The progression of the infection will lead to bone destruction, in parallel to sequestration (necrosis) of bone fragments (Sia and Berbari, 2006). In the advanced stages, subperiosteal abscesses are formed. Trueta's osteomyelitis hypothesis explains the pathogenesis as a haematogenous infection that starts along the metaphysis of the long bones and spreads to reach the cortex, causing lifting of the periosteum due to subperiosteal abscess (Weenders *et al*., 2015).

Diagnosis

Patients with osteomyelitis usually report variable symptoms, such as pain, sweating, lack of motility, weight loss and significant increase in body temperature (>38°C). These symptoms could be sufficient for the physician to make the diagnosis and start early treatment with antibiotics. Microbiological investigations can support the final diagnosis (Lima *et al*., 2014). Blood tests reveal increased levels of biomarkers (ESR and CRP) and leukocytes count. The synovial fluid examination indicates a high level of polymorphonuclear cells (Rosenberg and Khurana, 2016). Bone tissue samples could be sent for PCR analysis for rapid detection of the pathogen. Imaging methods, including ultrasound, show subperiosteal collection and sometimes joint effusion. However, these findings can be detected after the 3rd - 5th day of the infection (Hatzenbuehler and Pulling, 2011).

Antibiotic treatment

Treatment of osteomyelitis depends on the age of the patient, the microbial factor and the time of onset of the infection (acute or chronic). In most of the cases, the drugs are administered intravenously. In both adults and children, the empiric therapy starts with cephalosporin 3rd generation combined with Oxacillin (Lima *et al*., 2014). Alternative drug therapy in adults is Vancomycin along with Ciprofloxacin, and in children and infants, Oxacillin or Vancomycin together with aminoglycoside. Treatment in patients with MRSA consists of Vancomycin or Teicoplanin. Linezolid and Daptomycin can also be used (Frank and Tacconelli, 2012; Iqbal *et al*., 2017). The treatment of choice in anaerobic infections is Clindamycin. Alternative treatment of Metronidazole is administered every 8 hours in patients with Gram negative anaerobic infections. For enteric bacteria, quinolones are the drug of choice. In *P. aeruginosa* infections Ampicillin/sulbactam and Piperacillin/tazobactam are used. Other regimens include Imipinem and Meropenem for 4 to 6 weeks (Schildgen, 2018; Sia and Berbari, 2006). However, the antimicrobial treatment of osteomyelitis differs after a joint implantation surgery. Penicillin G intravenously or Ceftriaxone are provided for a period of 4 weeks followed by Amoxicillin in case of *Streptococcus spp*. infection. Intravenous Clindamycin is applied for 4 weeks in anaerobic infection then Clindamycin and Ciprofloxacin per os. The duration of therapy is at least 3 months in internal hip fixations and hip joint prosthesis, and up to 6 months in knee implants. Intravenous administration of antibiotics can be switched to oral therapy after stabilization of CRP level and normalization of leukocyte counts (Frank and Tacconelli, 2012). In diabetic patients and patients with vascular disorders oral treatment is contraindicated. Surgical management includes draining of abscess and removal of the necrotic tissues (Lima *et al*., 2014).

Microbiological aspects of prosthetic joint infection

Prosthetic joint infection (PJI) is a complication acquired mainly after a joint arthroplasty of shoulder, knee or elbow joints (Vaishya *et al*., 2019). Gram positive bacteria, along with Gram negative and anaerobes, are considered to be the most common etiological factors, with the predominant role of *P. acnes*, especially after surgery in the

upper part of the body (Kadler *et al*., 2015; Shah *et al*., 2015). The route of infection in PJI is through direct inoculation of the pathogen into the blood stream or via haematogenous spread. The formation of biofilm helps the microorganism to become more resilient. Diagnosis requires data collection from clinical symptoms, results from microbiological investigations along with imaging methods. The treatment in PJI includes antibiotics, together with surgical management (Tande and Patel, 2014; Vaishya *et al*., 2019).

Aetiology

The microbial agent highly correlates with the post-operative period of the patient after on-going surgery. In the early period, 3 months after the surgery, *S. aureus*, beta-haemolytic streptococci and enterococci were found to be strongly associated with the infection. At a later period, 3 to 24 months after the surgery, *P. acnes* was found to be the leading factor of PJI, and in the late period after the surgery Gram negative rods, originating from infectious focus elsewhere, such as respiratory and urinary tract infection, are usually detected (Tande and Patel, 2014; Shah *et al*., 2015; Vaishya *et al*., 2019).

Risk factors

Age plays a major role in the induction of PJI. Elderly patients are more predisposed to the infection. Male gender, increased androgens levels, diabetes mellitus, ulcers, traumas, open wounds, previous surgical procedures, urinary tract infection, enteritis, prolonged term of corticosteroid abuse, drugs and bacteraemia are also in the category of risk factors for PIJ (Tande and Patel, 2014).

Pathogenesis

PJI is caused mainly by direct contamination of the surgical site by the pathogenic organism. Other routes of infection include direct inoculation from infection elsewhere. In PJI, microorganisms usually form a biofilm, which adheres to the prosthesis, causing alteration in the host defensive mechanism. As a consequence, the microbial agent tends to be more resistant to antibiotics and surgical removal of the biofilms will be required (Tande and Patel, 2014; Shah *et al*., 2015; Vaishya *et al*., 2019).

Diagnosis

The diagnosis of PJI includes the clinical symptoms and the complaints reported by the patient, supported by the results from microbiological investigation and imaging methods. The clinical presentation includes general symptoms of pain, fever and motion weakness. However, the clinical picture remains general and unspecific. To confirm the final diagnosis, microbiological investigations are required. Blood samples reveal increased levels of inflammatory biomarkers (CRP, ESR) and white blood cells (Vaishya *et al*., 2019). Swab cultures from wound drainage help in the diagnosis of deep bacterial infection, as well as prosthetic components (Larsen *et al*., 2012). High levels of cytokines including IL-6 can be detected using synovial fluid culture. Alpha-defensin is considered to be an important biomarker in prosthetic joint infection (Larsen *et al*., 2012; Perry and Hanssen, 2017; Vaishya *et al*., 2019).

Antibiotic treatment

The treatment of PJI includes intravenous antibiotics. In case of biofilm formation, the treatment starts with disruption and removal of the biofilm by surgical debridement. The surgical debridement alone cannot achieve a total healing process. Cephalosporins 1st generation and penicillins are the drugs of choice. Rifampicin combined with Daptomycin is highly associated with higher cure rate. In the case of *P. acnes* PJI, primary treatment starts with Penicillin or Ceftriaxone. Vancomycin and Clindamycin are alternative first line drugs (Frank and Tacconelli, 2012; Tande and Patel, 2014; Schildgen, 2018).

Discussion

Many etiological factors are considered to be causative agents for these types of infection. *S. aureus* is the most commonly reported agent, especially in children (64.3%) (Sia and Berbari, 2006; Brankov *et al*., 2007; Colston and Atkins, 2018).

In 2007, a team of the University Hospital "N. I. Pirogov", Sofia, Bulgaria, reported a study of 49 children with haematogenic osteomyelitis. Only in 14 of the cases microbiological aethiology was proved. The leading causative agent was *S. aureus*, followed by *S. pyogenes*, *Proteus spp*. and *Pyocianeus spp*. (Brankov *et al*., 2007).

In the largest Bulgarian university hospital – "Saint George", Plovdiv, *S. aureus* is also the leading causative agent in orthopaedic infections, followed by *Acinetobacter spp* and members of order *Enterobacterales*, such as *E. coli* and *Enterobacter spp*. Gram negative bacteria are reported to be more involved in causing post-surgical orthopaedic infection in comparison with Gram positive and other infectious agents (Table 3), (Murdjeva *et al*., 2018). For the period January 2017 - August 2018, the relative part of Gram negative bacteria associated with post-surgical orthopaedic infections is 63.1%.

Table 3. Aetiology of post-surgical infections in orthopaedic patients from University hospital "St. George" - Plovdiv

Microorganism	Number of isolates for the period Jan 2017-Aug 2018
S. aureus	49 (26%)
CNS	10 (5%)
Acinetobacter spp.	31(16%)
P. aeruginosa	17 (9%)
Stenotrophomonas maltophilia	1 (0.5%)
E. coli	24 (13%)
Enterobacter spp.	26 (14%)
Proteus spp., Morganella spp.	11 (6%)
Klebsiella spp.	6 (3%)
Serratia marcescens, Citrobacter spp.	3 (1.6%)
Enterococcus spp.	7 (3.7%)
Streptococcus spp.	3 (1.6%)
Corynebacterium striatum	1 (0.5%)
Total number of isolates	189

Although very little information on osteomyelitis caused by Gram negative bacteria is available in the medical literature, a Brazilian study published in 2012 reported 101 cases of osteomyelitis caused by 121 bacteria belonging to this group. The samples were collected in the period January 2007 - January 2009. Of all the isolates, 25% were *Enterobacter spp*., 21% - *A. baumanni*, and 20% - *P. aeruginosa* (De Carvalho *et al*., 2012).

A British study published in 2013 reported seventy-nine patients with haematogenous vertebral osteomyelitis (HVO). Of them, 10 patients (12.66%) had Gram negative bacteria isolated. These microorganisms included *E. coli* (4 isolates), *P. aeruginosa* (3 isolates), *K. pneumoniae* (1 isolate), *H. Influenzae* (1 isolate) and *E. cloacae* (1 isolate) (Graham *et al*., 2013).

The treatment of Gram negative orthopaedic infections is often a challenging task because of unpredictable resistance patterns and limited published data on effective antimicrobial regimens.

Conclusion

Postsurgical infections in orthopaedics are serious conditions which require emergency treatment due to the life threatening complications they can cause in the human organism, such as neurological and vascular injury, sepsis, and death induction. Many risk factors contribute to the progression of the infection towards an irreversible stage. Numerous etiological agents, form different groups of bacteria, fungi and viruses are considered to be causative factors. To diagnose these infections, data from clinical symptoms, family history, microbiological investigations and imaging methods must be collected. Treatment is based mainly on intravenous antibiotics. Early treatment prevents postoperative complications. Antimicrobial therapy is not always efficient, in which case surgical procedures must be taken into consideration.

References

Brankov, O., T. Penushliev, T. Georgiev, S. Stoilov, M. Totev, M. Panov (2007). Acute hematogenous osteomyelitis in young children - clinical and radiological features. *Rentgenol. Radiol*. **46**: 257-260.

Buxton, R. A., M. Moran (2003). Septic arthritis of the hip in the infant and young child. *Curr. Orthop*. **17**: 458-464.

Colston, J., B. Atkins (2018). Bone and joint infection. *Clin. Med. J. R. Col. Physician. London* **18**: 150-154.

Combs, K., K. Cox (2018). Clinical outcomes involving patients that develop septic arthritis with methicillin sensitive Staphylococcus aureus versus methicillin resistant *Staphylococcus aureus. J. Orthop.* **15**: 9-12.

De Carvalho, V. C., P. R. D. De Oliveira, K. Dal-Paz, A. P. De Paula, C. da S. Félix, A. L. L. Munhoz Lima (2012). Gram-negative osteomyelitis: clinical and microbiological profile. *Brazilian J. Infect. Dis*. **16**: 63-67.

DiStefano, J. G., S. Pinney (2010). Ankle arthritis: etiology and epidemiology. *Semin. Arthroplasty* **21**: 218-222.

Frank, U., E. Tacconelli (2012). The Daschner Guide to In-Hospital Antibiotic Therapy, 2nd Edition, Springer, Switzerland, pp. 37-40.

Gaston, J. S. H., M. S. Lillicrap (2003). Arthritis associated with enteric infection. *Best Pract. Res. Clin. Rheumatol.* **17**: 219-239.

Goldenberg, D. L. (1998). Septic arthritis. *Lancet* **351**: 1060-1061.

Graham, S. M., A. Fishlock, P. Millner, J. Sandoe (2013). The management gram-negative bacterial haematogenous vertebral osteomyelitis: A case series of diagnosis, treatment and therapeutic outcomes. *Eur. Spine J*. **22**: 1845-1853.

Hatzenbuehler, J., T. J. Pulling (2011). Diagnosis and management of osteomyelitis. *Am. Fam. Physician*. **84**: 1027-1033.

Iqbal, H. J., N. Ponniah, S. Long, N. Rath, M. Kent (2017). Review of MRSA screening and antibiotics prophylaxis in orthopaedic trauma patients; the risk of surgical site infection with inadequate antibiotic prophylaxis in patients colonized with MRSA. *Injury* **48**: 1382-1387.

Kadler, B. K., S. S. Mehta, L. Funk (2015). *Propionibacterium acnes* infection after shoulder surgery. *Int. J. Shoulder Surg*. **9**: 139-144.

Kaplan, S. L. (2014). Recent lessons for the management of bone and joint infections. *J. Infect*. **S1**: 68

Kemper, C. A., S. C. Deresinski (2013). Fungal arthritis, Oxford Textbook of Rheumatology, 4nd Edition, Oxford University Press, pp. 808-814.

Larsen, L. H., J. Lange, Y. Xu, H. C. SchØnheyder (2012). Optimizing culture methods for diagnosis of prosthetic joint infections: A summary of modifications and improvements reported since 1995. *J. Med. Microbiol*. **61**: 309-316.

Lima, A. L. L., P. R. Oliveira, V. C. Carvalho, *et al* (2014) Recommendations for the treatment of osteomyelitis. *Brazilian J. Infect. Dis*. **18**: 526-534.

Lin, W. T., H. J. Tang, C. C. Lai, C. M. Chao (2017). Clinical manifestations and bacteriological features of culture-proven Gram-negative bacterial arthritis. *J. Microbiol. Immunol. Infect.* **50**: 527-531.

Marks, M., J. L. Marks (2016). Viral arthritis. *Clin. Med. J. R. Coll. Physic. London*. **16**: 129-134.

Mathew, A. J., V. Ravindran (2014). Infections and arthritis. *Best Pract. Res. Clin. Rheumatol.* **28**: 935-959.

Moro-Lago, I., G. Talavera, L. Moraleda, G. González-Morán (2017). Clinical presentation and treatment of septic arthritis in children. *Rev. Esp. Cir. Ortop. Traumatol*. **61**: 170-175.

Murdzheva, M., L. Paunov, A. Petrova (2018). Microbiological Aspects Of Joint And Bone-marrow Infections. *14th Congress of Microbiologists in Bulgaria with International Participation, Hisarya* **MM2**: 12.

Nade, S. (1977). Acute septic arthritis. *Bull. Postgrad. Comm. Med. Univ Sydney* **33**: 131-136.

Offiah, A. C. (2006). Acute osteomyelitis, septic arthritis and discitis: Differences between neonates and older children. *Eur. J. Radiol*. **60**: 221-232.

Perry, K. I., A. D. Hanssen (2017). Orthopaedic infection: Prevention and diagnosis. *J. Am. Acad. Orthopaed. Surg*. **25**: S4-S6

Qin, Y. F., Z. J. Li, H. Li (2018). Corticosteroids as adjunctive therapy with antibiotics in the treatment of children with septic arthritis: A meta-analysis. *Drug Des. Devel. Ther.* **12**: 2277-2284.

Rosenberg, A. E., J. S. Khurana (2016). Osteomyelitis and osteonecrosis. *Diagn. Histopathol*. **22**: 335-368.

Shah, N. B., A. J. Tande, R. Patel, E. F. Berbari (2015). Anaerobic prosthetic joint infection. *Anaerobe* **36**: 1-8.

Shirtliff, M. E., J. Le Frock (2003). Septic arthritis. *Musculoskeletal Infect*. **3**: 183-210.

Sia, I. G., E. F. Berbari (2006). Infection and musculoskeletal conditions: Osteomyelitis. *Best Pract. Res. Clin. Rheumatol*. **20**: 1065-1081.

Smith, J. W., P. Chalupa, M. S. Hasan (2006). Infectious arthritis: Clinical features, laboratory findings and treatment. *Clin. Microbiol. Infect*. **12**: 309-314.

Tande, A. J., R. Patel (2014). Prosthetic joint infection. *Clin. Microbiol. Rev.* **27**: 302-345.

ter Boo, G. J. A., D. W. Grijpma, T. F. Moriarty, R. G. Richards, D. Eglin (2015). Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. *Biomaterials* **52**: 113-125.

Vaishya, R., R. Sardana, H. Butta, L. Mendiratta (2019). Laboratory diagnosis of Prosthetic Joint Infections: Current concepts and present status. *J. Clin. Orthop. Trauma* **10**: 560-565.

Weenders, S. G. M., N. E. Janssen, G. W. D. Landman, F. P. van den Berg (2015). Subperiosteal abscess in a child. Trueta's osteomyelitis hypothesis undermined? *Orthop. Traumatol. Surg. Res*. **101**: 763-765.

Wilson, J. W., L. L. Estes (2012). Mayo Clinic Antimicrobial Therapy Quick Guide, 2nd Edition, Oxford Medicine, pp. 215-220.

Zekry, M., S. A. Shahban, T. El Gamal, S. Platt (2019). A literature review of the complications following anterior and posterior ankle arthroscopy. *Foot. Ankle Surg*. **25**: 553-558.