Microcephaly associated with Zika virus infection – prevention, diagnosis and treatment

also

Understanding tokophobia phenomenon as a key to proper management

How stress and anti-stress remedies influence bone health

Infective endocarditis caused by dental problems correlated with bicuspid aortic valve
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Symptoms of Zika virus (ZIKV) infection are usually mild and do not require aggressive management. For the same reason detection of ZIKV is not routinely performed. Unfortunately, consequences of inborn infections can be grave and lead to permanent disabilities. Association between ZIKV infection and microcephaly in infants was observed during the recent outbreaks. Range of clinical implications caused by microcephaly differs depending on the severity of condition. As targeted therapy is not available, management of future mothers is mostly focused on prevention of the infection. Most cases of ZIKV transmission are caused by vectors, therefore adequate use of protection against mosquitoes is essential. Planning pregnancy should be postponed in case of suspected infection – for 8 weeks and 6 months for women and men, respectively. Confirmation of infection is possible by detection of ZIKV, ZIKV RNA or any other antigen in bodily fluids or tissue and serological testing. Management of children with microcephaly requires advanced diagnosis considering their development and neurological condition together with early implementation of psychomotor therapy. The gravity of ZIKV infections in endemic populations manifests the need of public health programmes concerning family planning and monitoring ZIKV expansion to new territories.
Zika virus (ZIKV) is a mosquito-borne flavivirus, first identified in Uganda in 1947 in monkeys by researchers monitoring yellow fever [1]. Later virus was identified in humans in 1952 in Uganda and the United Republic of Tanzania [2]. Outbreaks of ZIKV disease have been recorded in Africa, the Americas, Asia and the Pacific [1]. From the 1960s to 1980s, human infections were found across Africa and Asia, typically accompanied by mild illness [1]. The first large outbreak of disease caused by Zika infection was reported from the Island of Yap (Federated States of Micronesia) in 2007 [2]. The next epidemic of ZIKV infection was reported in 2015 in South and Central America and the Caribbean [1].

TRANSMISSION
Apart from spreading by vectors, vertical transmission is also possible if woman’s infection occurs short before or during pregnancy [3]. Research is ongoing to determine the possibility and characteristics of transplacental ZIKV transmission [3]. Although the virus can be present in breast milk, no transmission of ZIKV through breastfeeding has been reported up to date [3]. ZIKV transmission may also, though rarely, occur through blood transfusion from a person in the period of viremia or sexually [3]. The maximum period of ZIKV presence in semen has not been ascertained, however it was confirmed to last over two weeks post infection [3]. It was also found that ZIKV may be present in urine and saliva, but so far no infection caused by contact with these bodily fluids has been described [4].

SYMPTOMS, DIAGNOSIS AND TREATMENT
The incubation period of ZIKV disease is not clear, but likely to be a few days [5]. People usually do not present enough symptoms to be admitted to the hospital and mortality associated with ZIKV infection is relatively low [6]. For this reason, many people might not realize they have been infected [6]. Symptoms of ZIKV infection are similar to other viruses spread through mosquito bites, like dengue and chikungunya [5]. The most common symptoms of Zika include: fever, rash, general pruritus, subcutaneous bleedings, joint pain and conjunctivitis [5]. Other symptoms are muscle pain, headache and loss of appetite [5]. These symptoms are usually mild and last for 2-7 days [7].

Due to real-time reverse transcription PCR (rRT-PCR) detection of ZIKV RNA is possible in various fluids: in serum (up to 6 days), urine (up to 27 days), cerebrospinal fluid (up to 7 days), saliva (up to 13 days), and vaginal swab (up to 13 days) [8]. Around the fifth day of the disease specific antibodies in blood are detected, but serological diagnosis can be difficult due to presence of cross-reactions with other flaviviruses [8]. Positive results in immunofluorescence screening tests must be confirmed by neutralization test (Plaque Reduction Neutralization Test - PRNT) [8]. To confirm the infection it is preferable to prove at least a 4-fold increase in ZIKV neutralizing antibodies titer, serum should be collected twice [8]. Treatment is mainly symptomatic. Usually, symptoms disappear spontaneously without complications. However, higher incidence of Guillain-Barré syndrome during ZIKV epidemics on the islands of French Polynesia was reported [6]. The direct relationship between the infection and the syndrome has not been definitively confirmed [6].

Treatment of ZIKV infection includes administration of antipyretics, but use of nonsteroidal anti-inflammatory drugs, especially acetylsalicylic acid, is not recommended until the exclusion of dengue [9].

MICROCEPHALY
Microcephaly is a neurological abnormality, usually congenital and presented at birth. It is defined as the head circumference at least 2 SD smaller than average for sex and age [10]. There are two main groups of microcephaly causes: genetic disorders (syndromes related to chromosomal or single gene defects) and acquired brain damages (intrauterine injuries, vertically transmitted infections, drugs and other) [11,12]. It was observed that newborns with microcephaly were also small for gestational age [13]. The prevalence of microcephaly ranges from 2.0 to 12.0 per 10000 live births (USA) and 2.9 per 10000 live births (Europe). There has been observed a significant change in the number of newborns born with microcephaly in Brazil as the prevalence increased from 0.6 per 10000 live births in 2010 to 4.2-8.2% in 2012-2015 in consequence of the outbreak of Zika virus infections [14].

INFECTION DURING PREGNANCY
ZIKV infection in pregnant women does not usually cause any grave disorder to mothers. The clinical manifestation consists of fever, maculopapular rash, arthralgia, fatigue, general malaise and other symptoms characteristic for viral infections [8,15]. Increased risk of microcephaly was associated with infections in the first trimester of pregnancy, similarly to other viral factors of congenital neurological disorders like Cytomegalovirus or Rubella virus [12]. Some data suggest that neurological abnormalities associated with ZIKV were also observed in infections with later onset during the second and even the third trimester of pregnancy [15].

PRENATAL DIAGNOSIS
In Brazilian case series, newborns of women infected with ZIKV between 5th and 16th week of pregnancy were affected by microcephaly [16]. Moreover, ZIKV genome was detectable in amniotic fluid samples [16,17]. Fetal microcephaly is usually diagnosed in ultrasound at 32.3 ± 5.1 week of pregnancy, however earlier observations are possible [16,18]. The ultrasound examination may show additional brain abnormalities. Except from the microcephaly, diffuse parenchymal calcifications, ventriculomegaly, reduced gyration and cerebellar hypoplasia were observed [1,18].

Neurological abnormalities typical for intrauterine ZIKV infection could be a cause of miscarriages or medical terminations of pregnancy [19,20]. Autopsies of infected fetuses confirmed microcephaly with fetal tissues positive
for ZIKV RNA, and viral antigens in glial cells and neurons [20].

**CLINICAL IMPLICATIONS OF MICROCEPHALY IN NEWBORNS**

Microcephaly is associated with various clinical problems which depend on how severe the microcephaly is [21]. Newborns with microcephaly may have developmental delay, intellectual disability, blurred vision, hearing loss, movement disorders, impaired coordination and balance, and difficulty swallowing [21]. Developmental delay concerns both speech and milestones such as sitting, standing or walking [21]. It is important to remember that severe microcephaly can be a life-threatening condition. It is very difficult to assess how advanced developmental disorder is and what kind of symptoms the child will present in future [21]. Because of this fact children with microcephaly should be checked up by doctors regularly [21].

**MANAGEMENT OF NEWBORNS WITH MICROCEPHALY**

Measurement of head circumference (HC), preferably within the first 24 hours of life, is the most common way of microcephaly diagnosis [21]. Specific growth charts are used for microcephaly assessment. The value for microcephaly on a HC centile chart is less than 3rd percentile or 2 standard deviations below the average [21]. There is no standard treatment for microcephaly. Procedures depend on how severe the microcephaly is. Children with mild microcephaly do not require any special care because their only symptom is smaller head size and they usually do not present additional clinical problems [21]. Newborns with severe microcephaly need early intervention which includes speech, hearing and physical therapies [21].

**TORCHZ ACRONYM**

Various observations suggest association between microcephaly and laboratory-confirmed ZIKV [13]. Detection of ZIKV specific IgM antibodies is an adequate method of congenital ZIKV infection diagnosis [13]. In Brazil significant association between epidemic of microcephaly and ZIKV infection was observed [13]. Therefore, it is suggested to extend the TORCH acronym [Toxoplasmosis, other infections such as Varicella-zoster virus, Syphilis, Parvovirus B1, Rubella, Cytomegalovirus and Herpes simplex virus] to TORCHZ acronym in order to pay attention to a serious problem of congenital ZIKV infection [13].

**RECOMMENDATIONS: PREGNANCY DURING ZIKV OUTBREAK**

Prevention of ZIKV infection during pregnancy includes avoiding travel to endemic areas and avoiding transmission via mosquito bites. Protection should focus on choosing proper clothing, covering arms and legs, use of registered insect repellents and staying in screened-in or air-conditioned rooms [22]. Laboratory evidence for ZIKV infection in pregnant women include detection of ZIKV, ZIKV RNA or antigen in any fluid or tissue, and positive serological test towards ZIKV with negative dengue results [23]. In a pregnant woman with confirmed ZIKV infection frequent ultrasounds are advised in order to monitor fetal anatomy and growth every 3–4 weeks. Patients should be managed by a perinatologist and infectious disease specialist [22].

**RECOMMENDATIONS: FAMILY PLANNING DURING ZIKV OUTBREAK**

Both men and women are advised to postpone procreation after likely ZIKV infection. For women it is recommended to wait at least 8 weeks after exposure or onset of symptoms. In case of men longer period – 6 months – is preferred. Couples planning pregnancy should avoid nonessential travel to areas with Zika, seek medical advice from healthcare provider, and prevent mosquito bites by means of repellents. Risk of sexual transmission can be decreased due to use of mechanical barriers [24].

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UNDERSTANDING TOKOPHOBIA PHENOMENON AS A KEY TO PROPER MANAGEMENT

Aleksandra Symonides¹, Izabella Mogilnicka¹, Katarzyna Krulak¹, Joanna Kacperczyk¹, Agnieszka Dobrowolska-Redo², Ewa Romejko-Wolniewicz²

1. Students’ Scientific Group affiliated to 2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Warsaw, Poland
2. 2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Warsaw, Poland

#Corresponding author: Aleksandra Symonides, e-mail: hsymonides@gmail.com, Warsaw Medical University, Karowa St 2, p.o. box 00-315 Warszawa, Poland, phone number: +48 22 596 64 21

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ABSTRACT

Tokophobia also known as fear of childbirth (FOC) becomes a frequent psychiatric indication to Caesarean section which makes it a rising problem of current obstetrics. Patients with FOC may suffer from additional psychiatric conditions such as depression. Women with higher risk of developing tokophobia are those with immense levels of fear of pain, young, with low educational level, poor socio-economic status, low self-esteem and lack of proper knowledge concerning peripartum period. History of unfortunate events during previous deliveries or illness of the older child are also associated with more frequent occurrence of FOC. Adequate management of FOC focuses on implementing psychotherapy. Symptoms of FOC can be decreased by means of qualified and trustworthy medical staff during labor or support from a closely related person. Secondary tokophobia can be prevented by minimalisation of negative experience during the first birth. If tokophobia is the symptom of depression, the underlying illness should be treated. Tokophobic patients are more prone to experience higher levels of pain during labor, which makes peripartum pain management harder for clinicians. FOC is one of the main reasons for performing caesarean delivery on maternal request (CDMR), which may lead to post-operative complications. Research shows that FOC is related to anxiety concerned with lower self-esteem due to changes occurring in women’s body during pregnancy and delivery. Learning and understanding the reasons behind tokophobia might lead to reducing the number of patients suffering from this condition and in consequence minimalizing the number of performed CDMR.
okophobia (from Greek toko meaning "birth" and phobos meaning "fear") is a fear of childbirth (FOC) and a variety of aspects related to it. Since the anxiety in the antenatal period is presented by up to 80% of women, tokophobia is defined as a pathological fear, exceeding the level observed in majority of patients, forcing 6-10% of women to avoid vaginal delivery and search for the possibility of Caesarean section (CS) [1].

So far, three types of this condition have been described: primary tokophobia, secondary tokophobia and tokophobia coexisting with depression. Primary tokophobia is characterized by an early onset, predating the pregnancy by years, sometimes as early as in adolescence, referring not only to the childbirth, but quite often to the pregnancy itself. Secondary tokophobia develops as a result of traumatic experience during earlier pregnancies (i.e. emergency CS, failure of analgesia). Patients suffering from tokophobia coexisting with depression present obsessive thoughts about risk of fatal complications during peripartum period or about being unable to give birth [1,2]. Women with tokophobia experience fear of possible pain and trauma they could be exposed to, but also of not being able to physically cope with the new experience, not receiving enough support or even perinatal death [1,3,4,5,6]. Tokophobia is one of the main reasons for performing caesarean delivery on maternal request (CDMR) and is described in the literature as psychiatric indication for performing CS [1,7,8,9]. The growing number of CSs is becoming the matter of concern for clinicians and governments. Only in Poland the percentage of the CSs doubled between 1999 (18.1%) and 2012 (37.0%) [10, 11].

CHARACTERISTICS OF PATIENTS WITH TOKOPHOBIA

Studies show that there are several features predisposing patients to development of tokophobia, among which are fear of pain, young age, low educational level, poor socio-economic status, low self-esteem, lack of proper knowledge, unfortunate events during previous deliveries or illness of the older child [1,4]. The fear of pain strictly correlates with sensitivity to it, which was proven by Saisto et al. – tokophobic patients are experiencing more intense pain than patients form control groups. Authors concluded that fear experienced by tokophobic patients leads to higher level of pain from which they suffer during delivery [12]. It was also observed that patients with FOC present lower levels of norepinephrine in response to painful stimuli than women from the control group [13]. In addition, tokophobia also leads to the labour lasting longer, with lengthening of the both first and second stage of labour up to 1/3 (10.5 vs 7.8 h, p=0.016 of the first stage and 42 vs 47 min., p=0.002 of the second stage) [14]. Moreover, women who needed surgical intervention during earlier pregnancies or those who required forceps or vacuum assistance during delivery, were more prone to developing tokophobia during next pregnancies [14].

In 2016 Hammama-Raz et al. compared intrapersonal and interpersonal factors which might have an impact on developing tokophobia. The data was collected from the Internet survey. 577 women over 18 years old with no serious mental or medical conditions completed online questionnaire. The demographic section of the survey included age, marital status, number of children and years of education. Participants were asked to provide information regarding relationship satisfaction, body image, self-esteem, life satisfaction, attitude towards pregnancy and birth, and FOC. Participants were divided into two groups, regarding whether they had or had not given birth before. None of the demographic factors was associated with tokophobia in the group of nulliparous women. Intra- and interpersonal characteristics were also insignificant in accordance to tokophobia. However, fear of body change and preventing body change by undergoing CS were positively associated with tokophobia and negatively with importance of pregnancy and birth. Attitude regarding the presence of the spouse during labour was not associated with FOC [15].

Among the parous group of participants, neither demographic, nor the inter- and intrapersonal characteristics were significant. The presence of the spouse during labour was also insignificant. However, attitudes toward pregnancy and birth, fear of body change, and considering adoption instead of natural birth were positively associated with tokophobia [15].

The fear of body change presented by women from both groups and its association with tokophobia might be linked with the beauty standards which are imposed by modern culture [16]. Women after pregnancy and birth are often less satisfied with their body image and feel less sexually attractive. Their identity changes from female to maternal [17]. The perspective of not fitting the strict beauty standards may cause anxiety, fear and lead to development of tokophobia [15].

Another important risk factor for FOC is history of abuse as women who reported sexual or physical abuse in childhood were more prone to higher levels of fear during birth, operative vaginal delivery and emergency CS [18].

Spice et al. examined the relationship between FOC and anxiety sensitivity (AS) [19]. 9% of women in their sample suffered from FOC which was comparable to rates of other researchers using the same method for FOC diagnosis - Wijma Delivery Expectancy/Experience Questionnaire [20,21]. Results showed that primiparous women were at higher risk of FOC than multiparous which confirmed previous findings [5,19,22,23]. Moreover, elevated trait anxiety was identified as a risk factor for experiencing FOC [19]. Eventually, AS was recognized as a significant predictor of FOC, separately from trait anxiety [19].

MANAGEMENT OF PATIENTS WITH TOKOPHOBIA

Both physical and psychological examination of patients with FOC is essential [19]. Physical complaints of women suffering from FOC may be symptomatic for fear and increased sensitivity to physical stimuli [2,13,19]. As Spice et al. suggests FOC can be predicted primarily in accordance to AS and is more strongly related to fear of pain rather than social consequences of anxiety.
symptoms [19]. Therefore, adequate quality and availability of peripartum analgesia is recommended. The need of analgesia and length of labour can be decreased due to presence of qualified medical staff and support from familiar person [24,25]. Fundamental method of FOC management is psychotherapeutic intervention [1,2,6]. Establishing specialized teams including the physician, the midwife and the psychologist increases focus on early identification of patients at risk of developing FOC and implementing prophylaxis or proper management depending on patient’s individual needs [6]. Effective therapy leads to decrease in labour length, fear levels and prevents negative experience associated with childbirth in women with FOC [18,26].

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REFERENCES

HOW STRESS AND ANTI-STRESS REMEDIES INFLUENCE BONE HEALTH

Karolina Gasińska¹, Daniel Piątek², Jerzy Bednarski³, Michał Kos², Paweł Marzęda², Justyna Drankowska², Anna Boguszewska-Czubara²

1. Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, 8 Jaczewskiego Street, 20954 Lublin, Poland
2. Chair and Department of Medical Chemistry, Medical University of Lublin, 4A Chodźki Street, 20093 Lublin, Poland
3. Chair and Department of Rehabilitation and Orthopaedics, Medical University of Lublin, 8 Jaczewskiego Street, 20954 Lublin, Poland

#Corresponding author: Karolina Gasińska, karolina.gasinska@onet.eu, Independent Public Teaching Hospital No 4 in Lublin, Medical University of Lublin, 8 Jaczewskiego Street, 20954 Lublin, Poland, phone number: +48 726500111

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ABSTRACT
Various factors affect the increased risk of skeletal system disorders in the modern society. Chronic stress can be regarded as one of the causes of greatest importance. Epidemiological studies conducted by the World Health Organization (WHO) indicate that the level of stress in the society is constantly increasing. This phenomenon is particularly apparent in developed countries. Bone tissue loss affects not only the elderly, but also people of younger age. Studies have shown reduced bone mineral content (BMC) and bone mineral density (BMD) in people exposed to chronic stress and suffering from depression. These facts can be explained through the mechanism of action of glucocorticoids (GCs) on the bone. It reduces the content of inorganic substances in the bone, thereby weakening its strength. Additionally, important factors causing BMC and BMD to decrease include usage of drugs such as antidepressants, as well as addictions such as smoking. Metyrapone, an inhibitor of cortisol synthesis, has been found to increase serum BMC and osteocalcin (OC) levels and to promote bone formation. Moreover, Alzheimer’s disease (AD) patients using rivastigmine are at lower risk of developing hip fracture.
BACKGROUND

Various factors influence the increased risk of skeletal system disorders in modern society. Chronic stress can be regarded as one of the causes of greatest importance. It is well known that stress exerts negative effects on the human psyche, and contributes to development of many somatic diseases, such as myocardial infarction, coronary heart disease, stomach and duodenal ulcers [1]. Moreover, stress-induced dysregulation activates psychological factors, which increase the risk of cancer occurrence or its progression [2]. These factors can also affect bone tissue, leading to pathological changes [3]. The modern way of life is associated with very high levels of stress. Epidemiological studies conducted by the World Health Organization (WHO) indicate that the level of stress in the society is constantly increasing. It has also been stated that it correlates strictly with increased numbers of diagnosed depression [4]. This phenomenon is particularly apparent in developed countries due to the development of civilization, overload of duties, competition in professional work, high population density and many other factors [5]. Stress, whether physical (i.e. exertion, heat, cold, accidental or surgical trauma, burns), or emotional (i.e. pain, anxiety, excitement or depression) increases bodily demand for magnesium [6]. Magnesium converts vitamin D into its active form, facilitating its role in calcium absorption. Magnesium also stimulates the release of calcitonin, which helps preserve bone structure and draws calcium out of the blood and soft tissues back into the bones, reducing the likelihood of osteoporosis [7]. The relationship between chronic stress, depression and osteoporosis seems to be an interesting and significant problem that affects the quality of life of the society.

Chronic, unpredictable mild stress model (CUMS) [8,9] is the most frequently used animal experimental model of depression, considered one of the best models. It is evoked through inducing the state of anhedonia, which is the main symptom of depression in humans, by subjecting animals to long-term exposure to several mild, yet unpredictable stressors, such as constraint, inversion of light-darkness cycle, deprivation of water or food, wet litter. This method affects animal behavior as well as their nervous system, altering brain activity and function of neurons. All behavioral changes induced in animals in this model can be reversed by administration of antidepressants [10]. Therefore, the CUMS model can be applied to analyze the impact of psychological and pharmacological factors on bone tissue.

Loss of bone tissue affects not only the elderly, but also people of younger ages. It is facilitated by use of various drugs, including antidepressants, [11] or susceptibility to an addiction, e.g. smoking [12]. However, some drugs used in the therapy of depression may have positive impact on bone health [13, 14].

BONE REMODELING UNDER STRESS AND DEPRESSION

According to the definition, stress is any uncomfortable emotional experience accompanied by predictable biochemical, physiological and behavioral changes. Stress can affect people of all ages, genders and positions [15]. Some types of stress can be beneficial at times, although extreme amount of stress or prolonged stressful situations may carry consequences to one’s health and adversely affect cardiovascular system, central nervous system, neuroendocrine and immune systems. Research shows that untreated chronic stress can contribute to development of heart disease, high blood pressure, muscle pain, anxiety, insomnia, and obesity [16]. Improved methods of assessment and research design established a robust and causal association between stressful life events and major depressive disorder (MDD) [17]. MDD is a mental disorder characterized by a pervasive and persistent low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities [18]. The most common time of onset is between the ages of 20 and 30 years, with a delayed peak between 30 and 40 years of age. Understanding of the nature and causes of depression has evolved over the centuries, although this understanding is still incomplete and has left many aspects of depression as a subject for discussion and research. Proposed causes include psychological, psychosocial, biological and hereditary factors. Typically, people are treated with antidepressant medication and, in many cases, also receive counseling, particularly in a form of cognitive behavioral therapy [19].

Generally, researchers indicate that stress has negative impact on bone tissue [1, 20, 21]. The mechanism of this phenomenon is still not completely understood. Basing on the literature, it can be assumed that steroid hormones, more precisely glucocorticoids (GCs), play a key role in bone remodeling [22–24]. Cortisol is the most important human glucocorticoid secreted by the adrenal cortex. This hormone is essential to human survival and it is crucial for adaptation to stress. Thus, cortisol concentration appears to be an adequate indicator for mental stress as its level increases significantly in response to stressors [25–27]. Cortisol slows down the absorption of calcium from the intestines and enhances its excretion in urine. This leads to the development of osteopenia and osteoporosis. Progressive bone demineralization increases the risk of pathological fractures of long bones. The study conducted among a group of children at risk of acute and chronic stress has revealed that the growth process can be slowed down or even stopped under stress [28]. The effect on bones, especially on the epiphyseal plate, is exerted through various mechanisms, including increasing serum cortisol levels and an increased number of pro-inflammatory cytokines as well as decrease in insulin-like growth factor 1 levels. Another study included 23 patients with endogenous CS (17 women and 6 men, the mean age was 39.7 and 44.3 years, respectively) [29], 18 of which had pituitary adenomas and 5 were diagnosed with adrenal tumors. Measurements taken in the lumbar spine, femoral neck, shoulders, legs, trunk and the whole body, showed reduced content of inorganic substance, particularly pronounced in the trunk and the whole body. Bone mineral density (BMD) index and the level of serum osteocalcin (OC), a protein found in bone, secreted solely by osteoblasts, were also reduced. Hypercortisolism was the cause of these disorders, resulting in decreased bone formation and increased bone resorption. BMD loss was
also confirmed in the hips of former prisoners of war diagnosed with posttraumatic stress disorder [21]. Another study concerned bone mineral content (BMC) index among 45 girls [30]. The content of inorganic substance was measured in the spine and the body by dual-energy x-ray absorptiometry (DXA). Decreased values of BMC were found in patients suffering from anorexia. It has been proven that they had elevated levels of cortisol, due to psychosocial stress. The state of bone tissue was also evaluated in children suffering from acquired glomerulopathies [31]. One group of patients was treated with a corticosteroid, while the other group was labeled as non-corticosteroid. In 18 out of 25 children who had received corticosteroids, bone demineralization and reduced BMC index were observed. The values grew after discontinuation of the drug. No other bone disorders were detected in non-corticosteroid patients. Increase in GCs secretion in people suffering from MDD has been extensively described [32–34]. It causes decrease of BMD through the same mechanisms as stress. Thus, MDD may be considered a risk factor for osteoporosis development [35–37]. The correlation between MDD and BMD index was assessed in a group of 97 employees (41 women and 56 men). Depressive symptoms were measured using a Center for Epidemiologic Studies Depression scale. DXA method was used for the BDM measurements in the hip, femoral head, spine, wrist and the body using standardized procedures. The study showed that among all women (but not men) with augmentation of depressive symptoms, the values of BMD index decreased [38]. However, BMD reduction regardless of sex among people with depressive symptoms exposed to chronic stress at work was demonstrated in another study [39]. People suffering from depression are more prone to use of drugs than healthy individuals [40, 41]. The negative effects of some drugs on bone tissue have been extensively described. However, drugs may not only be the result of depression, but also put one at increased risk of its development [42]. These facts indicate that people suffering from depression and using antidepressant therapy may be more vulnerable to bone damage.

**RELATIONSHIP BETWEEN NICOTINE AND BONES**

Correlation between tobacco smoking and bone loss was has been stated more than 20 years ago. The negative impact gets worse when combined with other coexisting addictions, bad dietary habits and lack of physical activity [43]. Nicotine, well known as the pharmacologically active substance in tobacco, has become one of potential risk factors, which contribute to osteoporosis – a disruption of balance between osteoblast and osteoclast function [44]. There are two types of bone turnover markers: enzymes secreted by osteoclasts and osteoblasts, and structural proteins or their fragments either secreted by osteoblasts during bone formation or released in the process of bone collagen matrix degradation during bone resorption. These markers circulate in the blood and are excreted in urine. Their measurements provide a quantitative estimation of the current rate of bone remodeling as well as turnover [45]. The study carried out on a group of women revealed that nicotine is associated with lower osteocalcin levels. The osteocalcin level was 12% lower among smokers compared to non-smokers [46]. Another research on clonal rat calvarial osteogenic cells (ROB-C26), clonal mouse calvarial preosteoblastic cells (MC3T3–E1) and on osteoclast-like cells has shown that exposure to nicotine increased deposition of Ca²⁺ as well as alkaline phosphatase activity in ROB–C26. On the contrary, in MC3T3–E1 those parameters were diminished [47]. Nicotine interfered with osteoblast differentiation in osteoblast-like cells. Nicotine is an agonist of nicotinic receptor alpha-4 subunit located on human primary bone cells. The effects of nicotine on proliferation of these cells were found to be dose-dependent: at high levels (>1 mmol/L) antiproliferative and at very low levels (0.01-10 micromol/L) exerted stimulatory effects. Moreover, an increase of osteopontin, a bone matrix protein implicated in regulating resorption, was observed at low levels of nicotine [48]. Nicotine affects differently human periodontal ligament cells. It downregulates the expression of alkaline phosphatase, OC and osteopontin, but increases the number of RANKL (receptor activator of nuclear factor-kappa B ligand) receptors [49].

Numerous studies have shown a decrease in BMC and BMD caused by nicotine [50–53]. In the study on the relationship between nicotine and concentrations of serum calcium, vitamin D₃, phosphorus and parathyroid hormone, the last two parameters were higher in rats treated with high-dose (137 ± 10 ng/ml) than with low-dose (111 ± 7 ng/ml) nicotine. It suggests that nicotine action depends on its serum concentrations. Bone loss has been observed at concentrations more than twice as high as the average value measured in blood sera of smokers [54]. It is possible that not only nicotine, but also other tobacco components could be responsible for bone damage in smokers, which was proven in a study investigating the effect of passive smoking on BMD of lumbar spine and femur. It revealed a correlation between smoking and lower BMD [55]. Nicotine exposure influences cortisol concentration in saliva, which is higher among smokers in comparison to non-smokers. Furthermore, decrease in salivary cortisol is reported after smoking cessation [56]. No differences were observed between ex-smokers and never-smokers, suggesting that smoking has a short-term effect on the neuroendocrine system [57]. Thus, nicotine-cortisol-bone pathway seems to play great role in the etiology of osteoporosis [58].

Nicotine seems to affect also bone healing process after injuries and surgeries by causing osteoblast dysfunction, and therefore prolonged bone repair [59]. The study conducted on 48 rabbits proved that a 7–week period of nicotine exposure accelerates angiogenesis, but inhibits expression of bone morphogenetic protein 2 and bone healing [60]. It appears that the above-mentioned studies confirm the positive effect of nicotine on skin wound healing [61] and negative on bone healing [62, 63]. On the contrary, research carried out on a group of 16 rabbits showed no relationship between short-term exposure (8 weeks) to nicotine and the time needed to implant osteointegration in comparison to a control group exposed to placebo [64]. Further studies are required to
assess long-term influence of nicotine on bone metabolism.

EFFECT OF ANTIDEPRESSANTS ON BONES

The struggle with depressive disorders is now one of the most important healthcare challenges. In the United States 1 out of 10 people over 12 years of age uses antidepressant therapy [65]. Additionally, in the US and Europe antidepressants are taken by 10–25% of women and 5–20% of men aged 60 years and older. These antidepressants are mainly selective serotonin reuptake inhibitors (SSRIs) [66].

The study conducted among a group of 928 women aged 24 to 98 included a series of clinical tests and measurements of BMD in different parts of the body. The results showed a negative effect of antidepressants on BMD in all studied groups of bones in men, while body weight was <75–110 kg (depending on the type of bone) [67]. In another research 849 Australian men aged 24 to 98 years were examined using ultrasonic methods. 61 (7.2%) of participants had used antidepressants. A number of quantitative measurements of various parameters of the calcaneus were taken. The adverse drug effect, mainly SSRIs, on bone density was proven, and thus the link between use of antidepressants and reduced bone strength among patients weighing less than 90 kg was corroborated [11]. Body weight is the main determinant of the potency of antidepressants on BMD [11, 67]. A group of 1972 women over 42 years of age was divided into three categories: 331 new SSR1 users, 71 new tricyclic antidepressants (TCA) users and 1590 non-users (no SSRI or TCA use). The study did not point to an increase in a degree of bone loss, i.e., lower BMD, among middle-aged women taking SSRIs or TCAs [68]. The study, which included 8217 women aged above 69 years, demonstrated an increased risk of fracture in all types of the bones except for the ilium and the vertebrae among the participants taking SSRIs. Therapies with TCAs also increased the risk of non-vertebral fractures, but this phenomenon was partly explained by concomitant harmful factors [69]. Another research concerned hip fractures of 906422 Norway residents. Significant increase in susceptibility to bone fractures in people taking at least one type of antidepressant was found. The percentage increase in risk of damage amounted to 4.7%. SSRIs seemed to have the greatest impact [66]. Representatives of the TCA group, like amitriptyline or clomipramine, increased the risk of fractures depending on the dose; however, imipramine and nortriptyline had no effect [70]. In conclusion, in most studies, SSRIs had a negative impact on BMD [11, 66, 69, 71, 72]. However, drugs from the TCAs group did not seem to have a major effect on BMD [68, 70] or sometimes even had a positive one [71].

CHANGES IN BONES INDUCED BY METYRAPONE

Metyrapone is well known as an inhibitor of endogenous adrenal corticosteroid synthesis. It reduces the production of cortisol and corticosterone by inhibiting the 11β-hydroxylation reaction in the adrenal cortex. Chronic hypercortisolism induces a wide range of changes in body composition and it may result in osteoporosis. Thus, metyrapone is a diagnostic tool for testing hypothalamic-pituitary adrenocorticotropic hormone function. Besides, metyrapone is considered a drug of choice when rapid control of hypercortisolaemia is required [14].

Recent experimental study aimed to elucidate the effects of metyrapone on urinary free cortisol (UFC). UFC was normal in 57% of patients treated with metyrapone alone, 46%of whom also demonstrated clinical control of the disease [72]. Experimental data suggests that metyrapone has a complex impact on bone turnover in swine and it favors anabolic bone metabolism. Elevated OC concentration was strictly limited to the period of metyrapone application. OC increased immediately by 7% one day after commencement of treatment. Accordingly, a decrease to control levels started after withdrawal of metyrapone, though overall concentrations were still slightly higher during the first week after the treatment [73]. Another study reveals that metyrapone administration failed to induce significant changes in OC levels. As regards serum OC, it is secreted by osteoblasts and it has been used in order to estimate the osteoblast activity rate. There were also no significant differences in terms of β-isomerized C-termpinal telopeptides (β–CTx) concentrations enabling assessment of the rate of osteoclast activity [74]. Moreover, metyrapone prevented bone loss by increasing the BMC of the metaphysis in diabetic mice. Noteworthy is the fact that the increase of serum corticosterone levels is independent of the etiology of bone loss, therefore, metyrapone may play an important role in treating a variety of metabolic bone diseases [75]. Another issue that is especially worth mentioning is such that corticosterone synthesis inhibitor – metyrapone, prevented stress-induced neurobehavioral changes. Furthermore, metyrapone prevented chronic, unpredictable stress-induced impairment of spatial memory consolidation [76]. Although metyrapone administration was well tolerated, it was ineffective in the treatment of refractory depression [77]. Further research should consider whether or not antiglucocorticoid treatments, such as metyrapone, should target patients with confirmed hypercortisolaemia.

THE TREATMENT OF DEMENTIA USING RIVASTIGMINE AND ITS IMPACT ON BONES

Rivastigmine is an acetylcholinesterase and butyrylcholinesterase inhibitor frequently used to treat AD [78]. The results of treatment with rivastigmine seem to be mediated exclusively by that process [79]. There is some evidence supporting a belief of clinical efficiency of rivastigmine in treatment of Levy body dementia, although studies do not give here a clear answer [80, 81]. AD is associated with an accelerated bone loss and lower BMD [13]. Moreover, recent meta-analysis demonstrated higher risk of hip fracture and lower hip BMD in AD patients [82]. The factor connecting AD and osteoporosis, according to the scientists, seems to be vitamin D3 deficiency. There are some observational, case-control studies showing an association between such a deficiency and AD [83]. Higher levels of OC, a marker of bone remodeling, were found in individuals with AD [84]. There is also inconsistent evidence on the role of
elevated level of osteoprotegerin as biomarker of AD risk, as some studies show the association [85] and some do not [84]. However, it is still not obvious whether the AD is the cause of these conditions or rather their effect [86]. The molecular mechanism connecting AD and bone loss leading to osteoporosis remains unclear. The study conducted on the group of 46 ambulatory female patients suffering from AD suggests malnutrition and sun deprivation as main factors of low 25(OH) D concentration and thereby loss of bone mass [87]. Nonetheless, there is also a hypothesis, that bone loss in AD can be mediated by central mechanisms corresponding to the atrophy of neurons of the parasympathetic nervous system in this neurodegenerative disorder [13].

Information on rivastigmine administration and its impact on bones isare limited. The results of case-control retrospective study conducted on 80 hip fracture patients with AD and the control group of 2178 AD patients without such fractures, suggest, that individuals using rivastigmine are at lower risk of developing hip fracture and the effect is dose-dependent [88]. The outcome of the study should not be bound to a lower incidence of falls, because the evidence seems to show quite the opposite, as syncope-associated falls are more prevalent in the group of patients treated with acetylcholinesterase inhibitors (AChEIs) [89]. AChEIs use can be associated with an enhanced fracture healing and minimal complications. A retrospective cohort study on 46 female AD patients, of whom 24 were AChEIs users and the remaining subjects were non-users, also showed better bone quality among treated patients [90]. Improvement in quality of bone tissue seems to be the effect of improved cholinergic neuron activity in AChEI-treated patients. The activity of parasympathetic nervous system is supposed to have profound impact on the process of bone remodeling and seems to save bone tissue from the activity of osteoclasts [88, 90]. Moving on to possible connotations of rivastigmine and stress, there is a case series reporting dramatic reduction of chronic posttraumatic stress disorder symptoms in 3 Iranian male patients. Using rivastigmine is suggested as a possible add-on to treatment of such a disorder, even though more tests are required to confirm these findings and determine whether it was the effect of improvement in cognitive status or rather cholinergic-adrenergic balance [91]. As mentioned above, high level of stress is a risk factor of demineralization, therefore lowering its level can make rivastigmine even more valuable in bone protection [92]. So far, neither clinical nor animal studies were conducted in order to investigate rivastigmine and its association with blood levels of specific bone turnover markers. Such a study could shed light on likely mechanisms of rivastigmin’s beneficial effect in aforementioned studies.

SUMMARY

Nowadays people are increasingly exposed to multiple stressors. Studies demonstrated that stress increases neuroendocrine hormones, particularly glucocorticoids and catecholamines, but to some extent also prolactin, growth hormone and nerve growth factor. Stress, through the action of these stress hormones, has detrimental effect on immune function, including reduced NK cell activity, lymphocyte population, lymphocyte proliferation, antibody production and reactivation of latent viral infections. Such effects on the immune system have severe consequences on health, which include delayed wound healing, impaired responses to vaccination as well as development and progression of cancer [93]. Major life stressors, especially those involving interpersonal stress and social rejection, are among the strongest proximal risk factors for mental disorders, especially MDD [94–96]. Both stress and MDD affect bones, causing reduction in bone strength and therefore, increased risk of fractures [97]. Vitamin D₃ and calcium supplementation are recommended in people at increased risk of pathological bone changes [98]. It is very important to increase the amount of dairy products in the diet [99] and regularly control bone condition with DXA and FRAX examinations [100].

Nicotine may be an important cause of decrease of BMC and BMD [45–47]. According to WHO data from 2015, nearly 80% of more than 1 billion smokers worldwide live in low- and middle-income countries. Thus, these populations are especially exposed to bone damage [101]. It is noteworthy that nicotine has been found to inhibit bone healing. Drugs currently used in medicine to counteract stress and depression, including antidepressants, may also reduce the amount of inorganic substance in the bone [67]. The impact of antidepressants is especially significant as their consumption has increased significantly in most countries since 2000 [102]. Prevention of depression at the same time could be the most effective way to prevent adverse changes in the skeletal system among patients using antidepressants. Metyrapone, inhibitor of cortisol synthesis, is used in the differential diagnosis of Cushing’s syndrome caused by adrenal adenoma, ectopic ACTH/CRH syndrome, Cushing’s disease, and adrenal hyperplasia. Metyrapone has been found to increase BMC and OC level, and to favor bone formation [74, 76]. Recent research indicated that certain neurons can regulate bone metabolism and that their damage results in worsening of bone health. Rivastigmine, acetylcholinesterase and butyrylcholinesterase inhibitor frequently used to treat AD is a drug that possibly could increase the activity of bone-regulating neurons. Use of rivastigmine is associated with a beneficial effect on bone strength and a decreased risk of hip fracture, likely through this mechanism. Even though more tests are required to confirm these findings, the fact that rivastigmine has been proven safe will facilitate clinical trials aimed at treating patients suffering from osteoporosis [88]. Further studies are required to assess long-term stress, nicotine and drug influence on bone metabolism.

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ABBREVIATIONS

AchEIs - acetylcholinesterase inhibitors
AD - Alzheimer’s disease
BMC - bone mineral content
BMD - bone mineral density
CUMS - chronic, unpredictable mild stress model
DXA - dual-energy x-ray absorptiometry
Gcs - glucocorticoids
MDD - major depressive disorder
OC - osteocalcin
RANKL - receptor activator of nuclear factor-kappa B ligand
SSRIs - selective seroton receptor inhibitors
TCA - tricyclic antidepressants
UFC - urinary free cortisol
WHO - World Health Organization
β–CTX - β-isomerized C-terminal telopeptides

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INFECTIVE ENDOCARDITIS CAUSED BY DENTAL PROBLEMS CORRELATED WITH BICUSPID AORTIC VALVE.

Sebastian Sawonik², Magdalena Rejmak², Ph. D. Marek Prasał¹
1. The Department of Cardiology, Medical University of Lublin.
2. Students’ Science Club affiliated at the Department of Cardiology, Medical University of Lublin.
The Head of the Department: Prof. Andrzej Wysokiński

# Corresponding author: Sebastian Sawonik, e-mail: ortalionik@wp.pl, Students’ Science Club affiliated at the Department of Cardiology, Medical University of Lublin, K. Jazewskiego St 8, p.o. box 20-090 Lublin, Poland; phone: +48 534959836

RUNNING TITLE Infective endocarditis correlated with bicuspid aortic valve.

KEYWORDS endocarditis, aortic valve regurgitation, infection.

WORD COUNT 911

CONFLICT OF INTERESTS no conflict of interest

ABSTRACT
The aim of the study was to emphasize the importance of prophylaxis of infective endocarditis. Also, the influence of heart failure and bacterial etiology on the treatment was analyzed. This study presents a case report of a patient who was suffering from IE. He was treated in the Cardiology Ward at the Medical University of Lublin. 47-year-old man has resected his tooth in a dental surgery. After a few days at home, he presented non-specific symptoms like fever and chest pain. Bicuspid aortic valve was diagnosed at the Cardiology Ward. Furthermore, vegetation on aortic valve was recorded in echocardiography. That is why IE diagnosis was made. After the therapy with Vancomycin, vegetation on aortic valve was still present. Regurgitation in 3rd state was developed by the patient. New valve was implanted. A few days after operation the patient had subfebrile state. He was treated with Vancomycin and Clindamycin. Currently, he is receiving ciprofloxacin as prophylaxis of IE. Heart failure is a risk factor of IE. These patients should get antibiotic prophylaxis before dental surgery. Patients with heart defect can develop more severe type and treatment in these cases is more difficult. Everyone should undergo non-specific prophylaxis of infective endocarditis.
E
ndocarditis is an inflammation of the inner tissues of a heart. It may include one or more heart valves, the mural endocardium, or a septal defect. Its intracardiac effects include severe valvular insufficiency, which may lead to intractable congestive heart failure and myocardial abscesses. If left untreated, IE is generally fatal [1]. Infective endocarditis usually concerns aortic valve or mitral valve, rarely tricuspid valve (correlated with drug addiction). Very rarely IE involves ventricles, atria and endothelium of great vessels in the thorax (for example aortic coarctation). It is sometimes caused by extraneous factor such as electrodes of heart pacemaker. Bacteremia precedes infective endocarditis (about 2 weeks in 80% of cases and it sometimes ranges from 2 to 5 months). Bacterial etiology constitutes 90% of cases. Approximately 70% of infections in NVE are caused by Streptococcus species, including S viridans, Streptococcus bovis, and enterococci. Staphylococcus species cause 25% of cases and generally demonstrate a more aggressive acute course (see the images below) [1]. In the past, Streptococcus viridans was the most frequent reason of infective endocarditis affecting natural valve. Less often these were Enterococcus spp., Chlamydia, Mycoplasma. In 10% of cases etiological factor cannot be found.

The most common symptoms are: high fever, joint pain, myalgia, astia, nausea, night sweats, asthenia, petechiae weight loss and shivers [2]. Murmurs can be found in 80% of cases during auscultation [3]. Sometimes there could be pneumonia, pulmonary embolism, or ecchymosis. Diagnosis can be established as definite IE, possible/rejected IE or rejected IE. To make definite diagnosis we need two major criteria, or 1 major and 3 minor criteria, or 5 minor criteria [4]. Criteria of IE and diagnostic algorithm can be seen in the diagram below.

The aim of the study was to analyze the case of infective endocarditis in the context of the most frequent etiology and the results of treatment. Furthermore, we wanted to emphasize the importance of prophylaxis of common cases in the future.

MATERIAL AND METHODS
The study involved a case of a patient treated in the Cardiology Ward at the Medical University of Lublin. Attention was paid to the initial symptoms, diagnosis, treatment and prognosis. Complications were compared with available literature.

RESULTS
A 47–year-old man has a tooth resection in a dental surgery. After two days at home he suffered from malaise, fever, shivers and chest pain. After his visit in a GP office he was admitted to the Cardiology Ward on 17th April 2007. Vegetation on the aortic valve was discovered with the use of echocardiography. Moreover, it turned out that the aortic valve was bicuspis, which could constitute a risk factor of infective endocarditis. IE diagnosis was made. Unfortunately, hemoculture was negative and it resulted in empiric antibiotic therapy. The patient was treated with Vancomycin. Since he was allergic to acetaminophen, which he had taken at home, he developed toxic and allergic dermatitis. That is why he received Prednisone, Calcium, Omeprazole, Lactobacillus acidophilus, Cilium and Methylprednisolone in ointment. As a result of IE, the patient developed aortic valve regurgitation at 3rd stage. On 3rd July 2007 the patient was transferred to Cardiosurgery Department, where artificial aortic valve was implanted. Results of laboratory tests before the operation were as follows: CRP: 28.68; WBC: 12530; creatinine 0.8 mg%; troponin I: 0.0 ng/ml. The surgery was conducted in precipitated procedure as a result of continued vegetation on aortic valve which was recorded in echocardiography. There were no complications during the procedure. After the operation Vancomycin treatment was continued. Starting with the 3rd day the patient had a sublebrile state peaking 38.6° C, CRP: 48.41; 59.90; 89.28 mg/l. There was no increase in the hemoculture test. Vancomycin, Clindamycin, Atenocumarol, Omeprazole, Spiranolactone, Atenolol, Lorazepam, Metamizol were ordered. INR was 2.0 – 3.0. On 26th July no vegetation was observed in echocardiography. The swab showed growth of Streptococcus viridians. Chest X-ray revealed cardiomegaly. Currently, the patient under the care of cardiology dispensary – CRP: 7.84 mg/l; INR: 2.6; WBC<4000. The patient is receiving Ciprofloxacin as prophylaxis of IE.

DISCUSSION
This research is important because it shows two problems arising while treating IE at the same time. First of them is bicuspis aortic valve (BAV). Patients with BAV have a higher tendency of Staphylococcal origin (38.9 vs. 21.5%. P=0.137), and 55.6% showed peri-valvular complications (TAV 16.1%, P=0.001) BAV was the only predictive factor of peri-valvular complications [5]. These patients usually require an early surgery which was confirmed by this case. Secondly, this case shows the importance of antibiotic prophylaxis of peri – dental procedures. However, other research shows the opposite: “In a large unselected cohort of patients with IE, the incidence of preceding dental procedures was minimal. The number of cases potentially preventable by means of AP was negligible” [6]. Our case proves that even if it is not a statistically important problem, it should be the subject of discussion in medical practice.

CONCLUSION
Antibiotic procedures must be limited to patients with the highest risk of IE (e.g. congenital heart disease) undergoing dental procedures. Amoxicillin or clindamycin are recommended antibiotics. The alarming thing is that a high number of people is not diagnosed and classified to the group of high risk of IE. That is why non-specific prevention is so important. Disinfection of wounds, dental and cutaneous hygiene, regular yearly dental follow-up (in high risk patients twice a year) and avoidance of piercing and tattooing are the examples of basic prophylaxis. On the other hand, patients with IE exposed to high risk factors can develop more complications of
therapy and additional treatment may be needed. Furthermore, non-specific symptoms like fever or chest pain, if persisting, require clinical tests.

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REFERENCES
4. Recommendations of Polish Society of Cardiology.

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Tab. 2. Recommended prophylaxis for dental procedures at risk. [7]
Tab. 3. Indications for echocardiography in suspected infective endocarditis. [7]
Tab. 4. Non-specific prevention measures should be applied to the general population and particularly reinforced in high – risk patients. [7]
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Tab. 6. ESC 2015 algorithm for diagnosis of IE. [7]
Tab. 7. Anatomic and echocardiographic definitions. [8]
### Tab. 3. Indications for Echocardiography in Suspected Infective Endocarditis

**Indications for echocardiography in suspected infective endocarditis**

- **Clinical suspicion of IE**
  - TTE
  - TOE
  - Prosthetic valve or intracardiac device
  - Non-diagnostic TTE
  - Positive TTE
  - Negative TTE

**Clinical suspicion of IE**

- **High**
  - TOE
  - TOE

- **Low**
  - TOE
  - TOE

*If initial TOE is negative but high suspicion for IE remains, repeat TTE and/or TOE within 5-7 days.*

TTE = transthoracic echocardiography; TOE = transesophageal echocardiography.

*TOE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unremarkable echocardiographic findings.*

### Tab. 4. Non-Specific Prevention Measures Should Be Applied to the General Population and Particularly Reinforced in High-Risk Patients

**Non-specific prevention measures should be applied to the general population and particularly reinforced in high-risk patients**

- Strict dental and cutaneous hygiene. Dental follow-up should be performed twice a year in high-risk patients and yearly in the others.
- Cleansing of wounds.
- Eradication or decrease of chronic bacterial carriage skin, urine.
- Curative antibiotics for any focus of bacterial infection.
- No self-medication with antibiotics.
- Strict aseptic control measures for any at-risk procedure.
- Discourage piercing and tattooing.
- Limit the use of infusion catheters and invasive procedure when possible favor peripheral over central catheters, and systemic replacement of the peripheral catheter every 3-4 days. Strict adherence to care bundles for central and peripheral cannulae should be performed.

### Tab. 5. Main Principles of Prevention of Infective Endocarditis

**Main principles of prevention of infective endocarditis**

1. The principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with previously known cardiac conditions is maintained.
2. Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest-risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucous).
   - Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
   - Patients with previous IE.
   - Patients with congenital heart disease.
   - Any cyanotic congenital heart disease.
   - Congenital heart disease repaired with prosthetic material whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if there remains residual shunt or valvular regurgitation.
3. Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
4. Aspecific measures are mandatory during various catheter manipulation and during any invasive procedures in order to reduce the rate of health-care-associated IE.

### Tab. 6. ESC 2015 Algorithm for Diagnosis of IE

**ESC 2015 algorithm for diagnosis of IE**

1. Repeat echo (TTE + TOE) microbiology
2. Imaging for embolic event
3. Cardiac CT
4. Imaging for embolic event

**Definite IE**

**Possible IE**

**Rejected IE**

**Definite IE**

**Possible IE**

**Rejected IE**

In summary, echocardiography, BC, and clinical features remain the cornerstone of diagnosis of IE. When BC are negative, further microbiological studies are needed. The sensitivity of Duke Criteria can be improved by new imaging modalities (MRI, CT, PET/CT) that allow the diagnosis of embolic events and of cardiac involvement when TTE/TOE are negative or doubtful. Those criteria are useful but they do not replace the clinical judgement of the 'Endocarditis Team'.
### Table 1: Anatomic and echocardiographic definitions (adapted from Habib et al.\(^\text{10}\) with permission)

<table>
<thead>
<tr>
<th>Surgery/necropsy</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vegetation</strong></td>
<td>Oscillating or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material.</td>
</tr>
<tr>
<td><strong>Abscess</strong></td>
<td>Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance.</td>
</tr>
<tr>
<td><strong>Pseudoaneurysm</strong></td>
<td>Pulsatile perivalvular echo-free space, with colour-Doppler flow detected.</td>
</tr>
<tr>
<td><strong>Perforation</strong></td>
<td>Interruption of endocardial tissue continuity traversed by colour-Doppler flow.</td>
</tr>
<tr>
<td><strong>Fistula</strong></td>
<td>Colour-Doppler communication between two neighbouring cavities through a perforation.</td>
</tr>
<tr>
<td><strong>Valve aneurysm</strong></td>
<td>Saccular bulging of valvular tissue.</td>
</tr>
<tr>
<td><strong>Dehiscence of a prosthetic valve</strong></td>
<td>Paravalvular regurgitation identified by TEE/TEE, with or without rocking motion of the prosthesis.</td>
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