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Българска медицина

Съдържание

Обзори

Оригинални статии

Доклад на случай

Изисквания към авторите

Bulgarian medicine

Content

Reviews

Original papers

Case report

Author's guidelines

ETIOLOGY AND PATHOGENESIS OF SPONTANEOUS BACTERIAL PERITONITIS

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ЕТИОЛОГИЯ И ПАТОГЕНЕЗА НА СПОНТАННИЯ БАКТЕРИАЛЕН ПЕРИТОНИТ

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РЕЗЮМЕ

Терминът спонтанен бактериален перитонит (СБП) е въведен от H.Conn през 1964 г. СБП е тежко усложнение на чернодробната цироза с асцит. СБП се превърна от опасно заболяване (със смъртност 90%) в лечимо усложнение на декомпенсираната цироза. Въпреки това, СБП е главна причина за смърт на пациентите с чернодробна цироза. СБП се определя като инфекция на асцитната течност (АТ) при отсъствие на съседен инфекциозен източник и/или интраабдоминално възпалително огнище. Всички пациен-

ABSTRACT

H.Conn first introduced the term spontaneous bacterial peritonitis (SBP) in 1964. SBP is a severe complication of liver cirrhosis with ascites. SBP has transformed from feared disease (with reported mortality of 90%) to treatable complication of decompensated cirrrhosis. Nevertheless SBP is the main cause of death in patients with liver cirrhosis. SBP is defined as the infection of ascitic fluid (AF) in the absence of a contigious source of infection and/or intraabdominal inflammatory focus. All patients with cirrhosis and ascites are at risk of SBP and the

ти с цироза и асцит са рискови за СБП, който се наблюдава в 10–15% от хоспитализираните болни. Около 50% от епизодите на СБП се възникват по време на хоспитализация. Литературният обзор е посветен върху етиологията и патогенезата на СБП. Грам-негативните чревни бактерии (E. coli и Klebsiella pneumoniae) са най-честите причинители на СБП. Съобщава се за увеличаване на случаите причинени от грам-позитивни микроорганизми. Бактериалният свръхрастеж, увреденият чревен пермеабилитет, бактериалната транслокация, бактериемията и имунните нарушения са главните механизми за колонизацията на АТ при болни с цироза.

Ключови думи: спонтанен бактериален перитонит, етиология, патогенеза, асцитна течност, чернодробна цироза.

prevalence of SBP is 10–15% in hospitalized patients. Around 50% of SBP episodes are present at the time of hospital admission. The review focuses upon etiology and pathogenesis of SBP. Gram-negative enteric bacteria (E. coli, Klebsiella pneumoniae) are the most common causative organisms (after bacterial translocation). Increased incidences of gram-positive organisms have been reported. Bacterial overgrowth, impaired intestinal permeability, bacterial translocatin, bacteriemia, immune disturbance are the main mechanisms for colonisation of AF in cirrhotic patients.

Key words: spontaneous bacterial peritonitis, etioligy, pathogenesis, ascitic fluid, cirrhosis hepatis.

SOCIAL SIGNIFICANCE

About 85% from cases with ascites in the United States are due to cirrhosis, but 60% from the patients in the hepatologic wards have cirrhosis and ascites (44). Liver cirrhosis is the 10-th in frequency reason for death in the United States (44). Spontaneous bacterial peritonitis (SBP) is a serious complication of patients with ascites (ascites is already considered to be a complication of cirrhosis, but not a decompensation) (44). Life of patients with cirrhosis and ascites at present is prolonged, so that 85% from them survive up to 1 year , 56%– 5 years (28). Nowadays it is well known, that the basic reason for the prolonged survival of patients with cirrhosis is the prophylactics and treatment of SBP and not using of nephrotoxic antibiotics (39). About 30–50% from the patients with cirrhosis die from some bacterial infection (11) – SBP (25–31%), pneumonia (15–21%), urinary tract infection (20–25%), bacteriemia (12%), soft tissue inflammations (11%) (1). For comparison- the lethality of hospital infection is 5–7% (11). SBP is the main reason for death in patients with cirrhosis (18). For the time being lethality from SBP has decreased from 80–90% to 20% (20), but in untreated patients it is still high (50–80%) (27).

DEFINITION

SBP is peritoneal infection , which is not caused by intra abdominal source (30) (perforation or abscess) , which needs surgical treatment (3).

SBP appears in sterile ascites (43). SBP is an intestinal disease (13).

HISTORY

The concept SBP is introduced relatively late from H. Conn in 1964 (25). Conn supported the idea of prolonged bacteriemia as a reason for SBP (30).

About half of periods of bacteriemia arise spontaneously (due to intestinal bacteria, penetrated before in the mesenteric lymph nodes by the so called bacterial translocation) (see below) , because of which the term Spontaneous Bacterial Peritonitis is introduced (43).

One of the most famous persons, who died from SBP is Ludwig van Beethoven (1827) (after total paracentesis and probable encephalopathy – he thought himself as Moses, seeing a lot of water around him). Later, lead was found in his hair, because lead was used illegally as sweetener and freshener of cheap wine at that time (34), which explains Beethoven's mysterious death.

Diagnosis

Internal Ascites Club recommends diagnosis of SBP to be assumed in the presence of Polymorfonuclear leucocytes (PMN) in ascites ≥250 mm^3 cells/mm^3, in spite the possibility for sterile bacterial culture, but the therapy would start empirical.

TERMINOLOGY

In cases when PMN are >250mm^3, but the cultures remain sterile, a new term is accepted – cultural negative neutrophilic ascites (CNNA). CNNA is viewed as a variant (synonym, equivalent) to SBP, because there is no significant difference in mortality (31). It is not mandatory in CNNA , the PMN is ascites to be >500 mm^3 (3). Positive bacterial cultures without increase in PMN >250/ mm^3 is defined as bacter ascites (BA). This condition is rare (about 5% among cases) and it's viewed as a stage (phase) of SBP (20,43).

FREQUENCY OF SBP

From 3,5–10% to 17,5–30% (averagely 10–15%) of the patients with cirrhosis and ascites have SBP (8,30). If we add to that amount the cases with CNNA, the frequency of SBP increases up to 19% (10–30%) (50). In 1/4 to 1/3 from the patients with cirrhosis and ascites there is a proof of presence of bacterial DNA in ascites (32). More than 25% of patients develop SBP till the third year after the initial appearance of ascites (between 7% and 30% per year) (41). SBP is more frequent (29–33%) in advanced hepatic disease with double increase of the serum bilirubin values and/or presence of albumin in the ascites <10g/l (25) (correlates with the opsonic activity of ascites) (3). SBP is rare in non-hospitalized patients (1,3%), but half (20) from the hospitalized patients with cirrhosis and ascites (26–50%) have SBP (similar to refractory ascites) (21,38,42). In our country the frequency of SBP is 9,7% from patients having cirrhosis with ascites (2).

SBP and stage of cirrhosis. SBP is observed almost always in advanced cirrhosis with ascites (70–85% from patients are in class C by Child-Pugh) (3), but according to other authors in class B, they are 51% (42), which leads to the conclusion , that SBP could be suspected in every cirrhosis with ascites- in class B or C. Peritonitis in cirrhoses class A (absence of ascites) most probably is secondary (25). Patients with SBP have average MELD score 24. MELD score is classification of hepatic disease in the last stage. Every point of MELD score increases the risk of SBP with 11% (38). In MELD >18 points, the risk of SBP is 30,6% (38).

PREDISPOSING FACTORS

The main risk factor for SBP is the advanced hepatic disease. Patients having cirrhosis class C by Child-Pugh develop SBP in 70% till the end of the first year.

The basic predisposing factors for developing SBP are hyperbilirubinemia, low values of prothrombin index (<40%), encephalopathy, febrile condition (21), hypoalbuminemia, low values of albumin in ascites (<10 g/l), portal hypertension (45) and bleeding from esophageal varices . When total value of albumin in ascites is <10 g/l, the risk of SBP is 10 times higher compared to cases with higher values (3).

The average values of HVPG (hepatic venous portal gradient) in SBP is 20,7mm Hg, whilst in ascites without SBP it is 17,6 mm Hg (45).

Bleeding from esophageal varices (one of the most common reasons for death in cirrhotic patients, especially with ascites) is a precondition for SBP (35). Haemorrhagia is the basic predisposing factor for SBP and other bacterial infections in 25–65% (20). More than 20% from patients with bleeding from esophageal varices have bacteriemia. The most common infection after endoscopic sclerotherapy (considerably less frequent after band) of esophageal varices is SBP (1). Although proton pump inhibitors (PPI) enhance the intestinal bacterial colonization, they increase bacterial overgrowth and microbial translocation in mesenteric lymph nodes, no association is established between application of PPI and SBP (15).

Refractory ascites can progress to SBP and hepatorenal syndrome (HRS) (22). Between 5% and 10% from the cirrhotic patients with ascites are on diuretic refractory or diuretic unremovable ascites, because of adverse reactions), but this frequency increases up to 50% during hospitalization (12). SBP is rarely combined with tense ascites.

When the ascites contains albumin <10g/l (1g/dl) 20% from patients develop SBP till the end of the first year, whilst in cases of higher values the frequency of SBP is 4% (4,11). The uncorrected with humanalbumin paracentesis of a large quantity of ascites (>51) is also a risk for SBP. Diuretic therapy increases the amount of albumin in the ascites and also the opsonization of micro organisms (4,11). However, other authors found higher frequency of SBP in patients treated with diuretics.

Hyponatriemia (<135 mmol/l) is frequent in tense and refractory ascites. Large volume paracentesis (>51) worsen renal function. Hyponatriemia is a prerequisite not only for SBP, but also for HRS and hepatic encephalopathy. Hyponatriemia < 130 mmol/l is observed in 1/5 of the patients with cirrhosis and ascites (7). Previous episodes of SBP increase the risk of the emergence of new.

SBP AND OTHER DISEASES

SBP is rarely observed in children having nephrotic syndrome, in patients with heart failure, in Budd-Chiari syndrome or in hepatic metastases. In these cases the content of albumin in ascites in considerably higher , than in patients with cirrhosis (20).

SECONDARY BACTERIAL PERITONITIS IN CIRRHOTIC PATIENTS WITH ASCITES

A reason for secondary peritonitis in these patients can be a rupture of umbilical hernia, diverticulum, colonoscopy, etc. Secondary peritonitis represents 5–15% from the cases with infected ascites (3). Mortality is higher.

ETIOLOGY

In 70–75% of cases , SBP is caused by gram-negative aerobic flora with small bowell origin (11,40), but the major cause are E.coli and Klebsiella pneumoniae (16). Less there have been found Enterobacter, Pseudomonas aeruginosa, Vibrio spp., Aeromonas, etc. (11). But after fluoro-quinolonic prophylactics of SBP, as well as in non-treated patients, gram-positive flora increases to 38–70% (4,11,21,40). Five are the most often isolated micro-organisms in Europe in SBP – E.coli (35–50%), Klebsiela pneumoniae (10–15%), Str.viridans (1–%), Str. Pneumoniae (4–5%), Aeromonas (4–5%) (40). Infections with Aeromonas and enterococci (3–5%) have worse prognosis (17). About 13–14% from cases in Europe there is isolated C.albicans (31). In the USA Streptococcus pneumoniae and Str. spp. are second in frequency causers of SBP (30%) after E.coli (46%) (3). In SBP only in 4 % (3,2%) (11) there are found anaerobes, whilst in secondary peritonitis – in 90%). Except this, bacterial flora is polymicrobial , compared to SBP, where it's monomicrobial in 92% (3).

In 2/3 of patients infection E.coli is caused from more pathogenic strain. Capsule antigen (mainly K1) is a polysaccharide , which determines the more severe course of SBP. The K1 antigen less activates the alternative path of activating of the complement (48). Most bacteria have to be opsonized with IgG or C3 and then they can be attacked by neutrophilic leukocytes (microphages) and macrophages (25).

After 1980 cases of SBP, caused by E.coli and Klebsiella species with wider spectrum of ß-lactamase production, become more frequent. These two causers affect only 7,5 % from patients having SBP, but they are often resistant to treatment with cephalosporines III generation (58% vs 13%) on the 72-nd hour from the beginning of treatment and morbidity on the 30-th day from the beginning of SBP is significantly higher (46% vs 15%) (47).

The relative part of coagulase negative staphylococcus increases from 16,7% to 35,6%; Staphylococcus aureus- from 11,1% to 17,8%, whilst this of E.coli and Klebsiela pneumoniae

decreases from 36,1% to 15,6% respectively and from 13,9% to 6,7% (4).

Another unfavorable indication is the increase of resistance of E.coli to cephalosporines III generation from 0% to 16% and of Staphylococcus aureus to fluoroquinolones from 25% to 50%. The resistance to ciprofloxacin is highest (40). Nosocomial infections with E.coli are not more frequent than community acquired infections in SBP, but their resistance against cephalosporines III generation is significant higher (77,8% vs 13,6%) (p= 0.001). The only currently active antibiotic against all micro-organisms is vancomycin (4). In the coming years epidemiological change is expected (metamorphosis) of SBP, not only in ethiology with increase of methicillin-resistant S. aureus, but also with occurrence of multiresistance, including such towards vancomycin (14).

Beside gastrointestinal tract, other possible sources for SBP are the lungs, the urinary tract, skin (venous system), etc. (5). In the presence of cirrhosis, lung infections with S.aureus and Str.pneumoniae are often. As opposed to SBP, urinary tract infections are even more frequent in cirrhoses in class B by Child-Pugh (52%) than in class C. Urinary tract infections, as well as SBP are also caused mainly from E.coli and Klebsiella pneumoniae (19). Bacteriuria is significant in 50% of patients with SBP and only in 10% of patients having sterile ascites (3,5,9).

PATHOGENESIS

The following consistency in pathogenesis of SBP is found: bacterial small bowel overgrowth – increased permeability of the intestinal barrier – bacterial translocation (BT) in mesenteric lymph nods (MLN)– occurrence of SBP with or without septicaemia (10). The bacterial small bowel overgrowth and BT are basic pathogenic conditions for SBP (25) , but according to some authors immune disorders have concurrent significance (as much as the BT) (30).

1.Bacterial small bowel overgrowth and intestinal permeability. Such a bacterial small bowel overgrowth is described in chronic liver diseases still in 1956 by G.Martini , as the frequency varies widely (20–75%) (15). The bacterial small bowel overgrowth is often observed in alcoholic cirrhosis (37,8% vs 13,3% in the control cirrhosis group) and in patients with ascites (37,1% vs 5,3% with ascites) (15). The bacterial small bowel overgrouth is more frequent in cirrhotic patients in class C by Child-Pugh (48,3%) compared to class B (27,0%) and class A (13,1%) (15).

Bile acids have powerful antibacterial action, but the bacterial small bowel overgrowth leads to their deconjugation (46).

Many studies have shown decreased gastric secretion in patients with cirrhosis. Malnutrition is a well-known reason for bacterial small bowel overgrowth, but it is ofter observed in cirrhosis , especially in advanced one (33). On the other hand , one manifestation of bacterial small bowel overgrowth is malabsorption (46).

Bacterial small bowel overgrowth can cause liver damage like alcoholic one (15). Deconjugated toxic bile acids increase metabolism of alcohol with accumulation of large quantities acetaldehyde (15). Bacterial small bowel overgrowth can worsen the present liver disease (15). Enteropathy in portal hypertension (swollen mucosa, intestinal stasis, hypomotility and intestinal congestion with decreased blood supply) and direct toxic effect of alcohol increases intestinal permeability (6).

Endotoxinaemia, sepsis and multiorgan failure also increases intestinal permeability (24).

2. Bacterial translocation (BT) in mesenteric lymph nodules. This term BT is accepted by R.Berg et al. in 1979 (33). The three basic factors for arising of BT in mesenteric lymph nodes (MLN) are bacterial small bowel overgrowth , decreased local immunity and impaired integrity of intestinal barrier (23,49). From MLN monobacterial flora (21) penetrates into ascites; in blood or both simultaneously (23). Bacteriemia is a bad

prognostic sign- mortality is 37,3% vs 12,7% in SBP without bacteriemia (p<0.001). Passage of microorganisms through the intestinal walls directly in peritoneal cavity without BT was not found, even experimentally (21).

Bacteria and their metabolites in MLN activate monocytes and lymphocytes (11). Microbial products (lipopolysaccharides) influence upon toll-like receptors (TLRs), which induce selective release proinflammatory cytokines (11) (TNF-a and IL-6). TLRs have a key role in innate immune response. There's a plenty in dendritic cells (J.Li et al., 2007). Increased production of cytokines in infections causes hyperdynamic portal blood flow and refractory arterial hypotonia (11), by increase of nitrous oxide (NO) (activating NO-synthetasis). Cytokines are increased in ascites and circulation in patients having cirrhosis, in a higher degree in more advanced cirrhoses (37). Cytokines worsen the passing of SBP (23). They increase systemic arterial vasodilatation (23), which is a precondition for arising of hepatorenal syndrome (HRS). In this way, TNF-a and IL-6 define the high hospital mortality (43) from SBP, which is due mainly to HRS.

SIRS (systemic inflammatory response syndrome) represents unballanced response to cytokines (11) and passes with sepsis and multiorgan failure (49).

3. Immune mechanisms. 1) In patients having cirrhosis the barrier function of the skin and mucosa is impaired. Skin is thin, oedematous and fragile. The impaired gastrointestinal motility increases mucous permeability; ulcerations arise and bacterial flora is changed. 2) Monocyte-macrophage system's (MMS) functions are reduced. Furthermore , blood surrounds liver „filter" by internal or external portosystemic shunts ; decreases the count and functions of Kupffer's cells; MMS's activity decreases; chemotaxis , phagocytosis and impaired production of cytokines ; survival of polymorphonuclear leucocytes (the macrophages) is decreased; their phagocytosis ability is decreased, chemotaxis , etc. 3) Cellular immunity is impaired. The complement decreases (C3,C4,CH50), opsonic ability and active protein C (11) . Opsonization of microorganisms is strongly correlated with the level of total protein in ascites (3). 4) Iatrogenic factors- invasive procedures (not including abdominal paracentesis) , immunosuppressive medications, PPI . 5) Others- malnutrition, alcohol (11).

4. Colonization of ascites. It appears in some of the periods of prolonged bacteriemia (26) – most often from MLV, but it is possible also from blood circulation. The basic factor for prolonged bacteriemia is reduced phagocyte activation of MMS, because of liver disease (25,43,51). Patients having cirrhosis are immunocompromised . Infections in these cases are often (29). Another important factor for bacteriemia ,as already emphasized , is the „surrounding" of liver „filter" by collateral blood circulation , due to portal hypertension (25,43), as well as by intrahepatic shunts (3). In advanced cirrhosis , the liver synthesis of C3 is decreased, but C3 is the most important factor for local defence in ascites and opsonization of bacteries , in order not to be attacked by neutrophilic leucocytes and macrophages (25). In SBP C3 in ascites has significantly lower values (7,3 ng/ml) compared to cases with non-infected ascites (16,4 ng/ml) (36). Apart from the impaired opsonization of micro-organisms , dysfunction of neutrophils occurs (51). Thereby antibacterial capacity of ascites and occurrence of SBP depend on liver function.

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Relationship between helicobacter pylori infection and gastroesophageal reflux disease

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Връзката хеликобактер – пилорна инфекция и гастроезофагеална рефлуксна болест

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РЕЗЮМЕ

Краткият литературен обзор е посветен на връзката между Хеликобактер-пилорна/ ХП / инфекция и Гастроезофагеална рефлуксна болест / ГЕРБ / ,които са често срещани социално-значими заболявания. Логично е, като се знае, че ХП въздейства и променя стомашната солно-киселa секреция, да се търси връзка между две киселинно обусловени състояния. Връзката е допускана, но търпи много противоречия и това я прави дискутабилна. Представени са доказателства „за“ и „против“ тази асоциация. Основна е дилемата, дали ХП инфекцията увеличава риска от развитието на ГЕРБ или протектира това заболяване.В последните години, в развитите страни се наблюдава тенденция на намаляване честотата на ХП и асоциираните с нея пептично-язвена болест и стомашен рак с нарастване честота на ГЕРБ. Натежават доказателствата, че връзката е негативна т.е. ХП статуса не повлиява развитието на симптомите, тежестта, рецидива, както и ефекта от лечението и усложненията на ГЕРБ.

Ключови думи: Хеликобактер-пилорна инфекция, ГЕРБ, връзка, Хеликобактер-пилорна ерадикация

ABSTRACT

This review article shows the relationship between Helicobacter pylori (HP) infection and gastroesophageal reflux disease (GERD), two socially important diseases with high incidence rate. As HP influences on and changes the stomach acid secretion it is logical to search for a relationship between these two acid-related diseases. Such a relationship has been supposed, however, it is very debatable and controversial. There is evidence against and for this association. A dilemma exists whether HP infection increases the risk of GERD development or protects the disease. In the recent years, in developed countries, there is a tendency of decreasing incidence rate HP infection and related peptic ulcer disease and gastric cancer and increasing incidence of GERD. There is evidence of negative feed-back, i. e. HP does not influence the symptoms, grade, recurrence and the effect of treatment and complications of GERD.

Key words: Helicobacter pylori infection, GERD, relationship, Helicobacter pylori eradication

Helicobacter pylori (HP) infects the stomach mucosa and leads to gastritis. HP infection often persists, induces chronic inflammation of stomach mucosa and leads to different diseases of gastrointestinal tract such as chronic active gastritis, atrophic gastritis, peptic ulcer disease (PUD), i. e. duodenal ulcer (DU) or stomach ulcer (SU), MALT lymphoma, and gastric cancer.[7]

HP infection changes the stomach acid secretion and affects the pathophysiology of gastroduodenal ulcer disease (GDUD[7] and gastroesophageal reflux disease (GERD)[5,8]. The relationship between PUD and HP infection is established and well-investigated in the literature[7]. Many investigations have been performed to explore the involvement of HP in the pathogenesis of GERD in patients with PUD based on the work of Labenz et al.[14], who studied HP positive patients with DU. The authors have established a higher incidence rate of esophagitis in patients who have conducted HP eradication than in patients in whom the infection persists. After that first pilot study there have been many others, some of them confirm Labenz et al.'s work, others lead to contradictory results.

The association between HP infection and GERD is still contradictory and debatable. HP infection and GERD are widespread worldwide and the co-existence of these two diseases is something expected. Thus a relationship between the diseases should be expected[4,5,8]. The relationship between atrophic gastritis due to HP infection and reflux esophagitis is examined. The results are contradictory.

Some authors find increase in reflux esophagitis after HP eradication,[23] others consider that HP infection protects the development of GERD or decreases its burden.[22] Few authors defend the hypothesis that HP increases the manifestation of GERD.[18]

DOES HP INFECTION LEAD TO GERD?

GERD impacts quality of life. The acid expression in the esophagus in patients with GERD is, probably, enough to induce endoscopic mucosal changes such as erosive esophagitis, ulcer, peptic esophageal stricture and Barrett's esophagus,[8,18,22]. It has been proved that HP can lead to GERD by different mechanisms:

- lower esophageal sphincter relaxation due to inflammation of stomach cardia
- increased acid secretion due to antral gastritis
- delayed stomach emptying
- production of cytokines which lead to esophageal epithelium damage[24]

The relationship between HP infection and the organism's own factors plays a significant role in the pathogenesis of GERD, too.

HP infection influences stomach acid secretion it two ways[5,24]. The limited inflammation of stomach antrum is associated with destruction of somatostatin secreting D-cells. Thus the negative feed-back on the acid stomach secretion is lost resulting in increase of parietal-cell mass and hyperchlorhydria which may increase the burden of esophagitis. On the other hand, the pangastritis which is associated with cytotoxic associated gene A (cag A) and vacuolizing cytotoxin (vac) leads to destruction of acid-secreting parietal cells in the corpus resulting in gastric atrophy with hypo- or achlorhydria, which may reduce the burden of GERD and its complications[24].

Meta-analyses from fourteen controlled clinical trials and another ten clinical trials confirm that HP negative status is associated with significantly increased risk of GERD[5]. This can be explained with the fact that individuals with predominantly antral HP infection have higher acid secretion and the probability to develop DU and/or GERD is higher. On the other hand, the acid secretion would be lower in individuals with HP infection predominantly in the corpus which may reduce the risk of development of GERD. Labenz is the first author who describes the influence of HP in the pathogenesis of GERD with PUD[8]. He shows an increased incidence rate of erosive esophagitis in patients with DU who had HP eradication (in 25%) in comparison with the group of patients who still are HP positive (in 12,9% of the cases). There are clinical trials that show HP eradication does not lead to

GERD. The statement that HP infection is protective or predisposing factor for development of GERD is controversial. It is established that neither the genotype, nor the gastric colonization are predictive factors of the organism for development of erosive esophagitis in patients with PUD one year after eradication.[2]

In summary, HP infection leads to gastric inflammatory response which could be antral or corporal depending on the HP strains, genetic and environmental factors.[10,24]

The role of HP infection in the development of GERD in the pediatric population was already confirmed.[18] It is found out that the incidence of reflux esophagitis, the biological marker for GERD, in HP positive patients is twice higher in comparison with HP negative patients. The risk of development of erosive esophagitis is by six times higher in HP positive patients than in HP negative ones. Reflux esophagitis is diagnosed in 100% of HP positive patients aged under 10 years.[18]

Significantly higher incidence rate of reflux esophagitis in HP positive patients is established, no matter of age and sex. These findings show that HP infection in children is positively linked with reflux esophagitis.[18]

The exact relation between HP and GERD is subject of permanent discussions. There exists clinical, endoscopic, manometric and pH-metric data showing the significant role of HP infection in the pathogenesis of GERD and reflux esophagitis. This finding is, however, no sufficient evidence of the relation between HP and GERD[17].

DOES HP INFECTION PROTECT FROM GERD?

It is considered that HP plays a protective role in the development of GERD by different mechanisms[24]:

- decrease of acid secretion due to chronic gastritis
- improvement of gastroesophageal junction due to proximal gastritis
- production of ammonia through HP colonization which is a potential stop in the system.

In several studies it is supposed that HP protects the development of GERD or reduces its severity[24]. A smaller number of studies suppose that the infection increases the manifestation of the disease. The incidence of HP infection in patients with GERD is lower than in those without GERD. Countries in which the incidence rate of HP infection is high present with a low incidence of GERD. The decreased incidence of HP infection and the associated diseases such as PUD and gastric cancer in the developed countries is related with the increased incidence of GERD.

Epidemiological investigations define the feed-back between HP infection and the incidence of GERD and its complications as Barrett's esophagus and esophageal adenocarcinoma[6]. Shama and Vakil[22] suppose negative feed-back between incidence of HP infection with cag A strains, Barrett's esophagus and esophageal adenocarcinoma.[22] Similarly, the consequences of GERD such as Barrett's esophagus and esophageal adenocarcinoma are less common in infected individuals, too.[21]

Studies in adults show that HP infection plays a protective role in the development of GERD by causing atrophic gastritis which leads to reduction of acid secretion. Gastric colonization with HP is a suspected protective factor against GERD.

A study from Taiwan[1,24] shows that only 33% of the patients with reflux esophagitis have HP infection compared to 67,5% of the patients with normal esophagus. The three virulent strains of HP infection are unknown among the patients with reflux esophagitis. In a study in Hong Kong, the incidence of HP infection in the patients with GERD is 34%. HP infected patients had less severe esophagitis than those who were not infected[1,23].

The incidence of HP infection is low in patients with reflux esophagitis whose treatment is based on inhibition of acid secretion and that

is why long-term therapy with PPI was prescribed.

In an American study[22] of HP infection with cag A strains it is established that the incidence of the infection is low in patients with Barrett's esophagus and cardial adenocarcinoma. The severe inflammation of gastric fundus is associated with reduction of acid secretion.

Contemporary studies on the inflammatory markers such as interleukins IL 1β and IL1RN show that proinflammatory genotypes may be protective against the development of GERD in HP infected patients. These genes play an important role in gastric acid secretion and visceral hypersensitivity of esophageal epithelium.

Strong negative feed-back between persistent HP antibodies, symptoms of GERD and the diagnosis of GERB in the population is found out. There is a hypothesis that the lack of HP infection may be associated with symptoms of GERD and its complications.

At a population level, HP and GERD are negatively associated and this is most outlined for cytoxin-associated gene product (cagA) positive strains of HP[11]. A review of 26 studies shows a rate of HP infection in patients with GERD of 39% compared with 50% in controls.[19]

Further studies are necessary to determine whether the HP eradication in children or early in adulthood is associated with increased risk of development of GERD. It is not known why only a small group of patients develop GERD or its complications and whether some infectious agents such as HP are a responsible precipitating factor. There are some potential mechanisms by which the lack of HP colonization may be associated with GERD:

- HP infection leads to gastric atrophy and direct suppression of acid production[4, 15, 17]. This effect is variable and in some cases results in increased acid secretion;[24]
- the lack of HP infection is associated with increased appetite and higher BMI which is a risk factor for GERD.

DOES THE RISK OF GERD INCREASE AFTER ERADICATION?

The effect of HP eradication on GERD is controversial. The HP eradication in patients with PUD is associated with increased risk of development of GERD compared with untreated patients[9]. Infection with HP cagA strains is associated with less severe GERD[9]

There are announcements from Japan and China for increasing acid secretion after HP eradication which leads to higher prevalence for reflux-esophagitis and does not exert any effect of the low dose of proton pump inhibitors (PPI) as a maintenance therapy.[1,11]

In a Japanese study[1] it is determined that the acid secretion increases after HP eradication with intensifying the reflux esophagitis and increasing its incidence. In contrast, there is data that reflux esophagitis is not influenced by HP eradication in patients with PUD of reflux esophagitis improves in patients with DU[11].

HP eradication in patients with PUD may be associated with increased risk of development of GERD compared with untreated patients.

Some studies show that HP eradication may lead to development of esophagitis or GERD associated symptoms. Other ones report an increase of GERD after HP eradication. There are studies that eradication of HP infection in populations of infected patients on average, neither causes, nor exacerbates GERD.[10,20,25]

WHAT IS THE INFLUENCE OF PPI ON THE DEVELOPMENT OF GERD?

Kuipers et al.[13] report that long-term PPI use may enhance gastritis and induce the progression of gastric mucosal atrophy in HP positive patients. The necessity of HP eradication in patients with reflux esophagitis and long-term PPI therapy is controversial. In another study, Kupiers et al.[12] examine the gastric atrophy progression in patients on long-term PPI therapy and they establish that there is no difference in progression between the patients with or without HP eradication. Investigations show the in-

creasing effect of PPI on intragastric pH in HP infected patients with GERD with rapid influence and decrease of retrosternal heartburn as well as its relation with the relapse. It has been summarized that the long-term efficacy of PPI maintenance treatment for GERD is not influenced by HP status.

The relationship between HP infection and GERD is debatable. The comparison between infected and not-infected patients shows that there is no difference whether the HP infection is associated with GERD. This is proved by 24-hours pH-metry, FGS and quality of life questionnaire. There is no clinically significant difference between HP infected and HP non-infected patients with GERD concerning the objective and subjective measurement of disease severity.[9] There are no clinically relevant proofs whether the HP infection is present in patient with GERD. According to Maastricht 3 consensus – 2005[15] and Maastricht 4 consensus-2010[16], the HP eradication does not concern the exit of the PPI treatment in patients with GERD. Thus routine testing for HP is not recommended in GERD patients.

Only in cases with prolonged acid suppression the extent of gastritis is influenced and corpus atrophic gastritis develops with the loss of the specialized glands that is accelerated. In these cases HP eradication is recommended. The guidelines of the American College of Gastroenterologist are similar.[3]

In conclusion, according to Maastricht 4 consensus – 2010, there is evidence that is competitive enough that HP status does not exert any effect on symptom severity, recurrence and treatment efficacy in GERD and its complications. The negative association is between the prevalence of HP and severity of GERD and incidence of esophageal adenocarcinoma.

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РЕЗЮМЕ

Vitamin D is a fat soluble nutrient and is one of the 24 micronutrients critical to human survival. It is found naturally in fish and eggs and is added to dairy products, but the sun is the major source. The body also produces it naturally from cholesterol with adequate amounts of UV light from sun exposure. Unfortunately there is only sufficient amounts of UV light coming from the sun when the UV index is 3 or higher; which only occurs year-round near the equator in between the 37th parallels. The skin also requires direct sun exposure so that the UVB rays can penetrate it.The RDA(Recommended Dietary Allowances- United States National Academies comprises four organizations – National Academy of Sciences (NAS);National Academy of Engineering (NAE);Institute of Medicine (IOM);National Research Council (NRC)) is currently set at 400–800 IU/daily but this is likely too low for adults. The safe upper limit in the United States is currently 2000 IU/daily and in Canada it's 4000 IU/daily. Research suggests that the safe upper limit is 10,000 IU/daily(**74**). Supplemental Vitamin D is implicated in wide-ranging benefits such as increased cognition, immune health, bone health, well-being, reducing the risk of cancer, heart disease, diabetes, multiple sclerosis, and also increasing testosterone levels in deficient populations.Serum levels below 20 nmol/L

ABSTRACT

In the last 5 years, there has been a remarkable change in our understanding of the health benefits of vitamin D. The classical actions of vitamin D as a determinant of mineral metabolism and rachitic bone disease have been expanded to include a broader role in skeletal homoeostasis and prevalent bone disorders such as osteoporosis. However, it is the nonskeletal function of vitamin D that has attracted most attention. Although pluripotent responses to vitamin D have been recognized for many years, our new perspective on nonclassical vitamin D function stems from two more recent concepts. The first is that impaired, vitamin D status is common to many populations across the globe. This has prompted studies to explore the health impact of suboptimal circulating levels of vitamin D, with association studies linking vitamin D 'insufficiency' to several chronic health problems including autoimmune and cardiovascular disease, hypertension and common cancers. In support of a broader role for vitamin D in human health, studies in vitro and using animal models have highlighted immunomodulatory and anticancer effects of vitamin D that appear to depend on localized activation of vitamin D. The conclusion from these reports is that many nonclassical actions of vitamin D are independent of conventional vitamin D endocrinology and are

indicates deficiency, between 20–50 nmol/L and indicates insufficiency. Many of the health benefits of Vitamin D begin at serum levels of 75nmol/L (**75**) It is best taken with meals or a source of fat (such as a meal or Fish Oil). There have been anecdotal reports of it causing trouble sleeping when taken later at night, so it might be best to take it earlier in the day (**62**).

therefore more sensitive to variations in vitamin D status. The current review summarizes these developments, with specific reference to the newly identified effects of vitamin D on the human health, but also highlights the challenges in translating these observations to clinical practice.

Key Words: Vitamin D,dosis,effects,benefits.

RECOMMENDED DOSAGE

At the end of 2010, the Institute of Medicine (IOM), an independent, nonprofit, nongovernment organization, based in the USA published the findings of a lengthy study to define the references values that best represent the levels of vitamin D and calcium that are optimal for human health(**62**)The select panel of scientists and clinicians that made up this IOM committee was faced with several challenges, not the least because the physiology and nutrition of vitamin D and calcium has for many years been intertwined. An additional challenge to any appraisal of vitamin D nutrition is the terminology that defines the various metabolites contributing to vitamin D physiology. The term 'vitamin D' specifically refers to the parental vitamin D produced endogenously by the action of sunlight on 7-dehydrocholesterol in skin (also known as vitamin D_3, or cholecalciferol), or obtained from dietary foodstuffs as either vitamin D_3 or vegetable vitamin D_2 (also known as ergocalciferol). Vitamin D derived from sunlight or diet undergoes metabolism, firstly to 25-hydroxyvitamin D (25OHD) that is the main circulating form of vitamin D used to define 'vitamin D status'. At physiological concentrations, 25OHD appears to be inactive as a signalling molecule. Consequently, the target cell function of vitamin D is determined by conversion of 25OHD to active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], which is catalysed by the vitamin D-activating enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1). The $1,25(OH)_2D$ produced in this manner then functions as a steroid hormone by binding to the nuclear vitamin D receptor (VDR) and acting as a regulator of gene transcription(**34**).

In the section of the IOM report that focuses specifically on vitamin D, the committee addressed four principal issues: (i) the health outcomes that are associated with vitamin D and its principal metabolites – pro-hormone 25OHD and active $1,25(OH)_2D$; (ii) the circulating level of vitamin D (or more precisely the serum concentration of 25OHD) that is optimal for these health outcomes; (iii) the daily intake of vitamin D required to achieve and maintain optimal vitamin D (25OHD) status; (iv) the likelihood of adverse side-effects from vitamin D supplementation. The report concluded that classical effects on skeletal homoeostasis remained the most clinically robust health outcome associated with vitamin D(**62**). Based on this, the IOM suggested that a serum level of 50 nmol/L 25OHD was sufficient to optimize bone mineral density (BMD) as a marker of skeletal health for most populations in the United States and Canada. However, the IOM did acknowledge that people with darker skin pigmentation (for whom UV-light induction of epidermal vitamin D production is less efficient) and those living at more Northerly latitudes may find it harder to meet this target level. This may be particularly relevant to populations in Northern Europe, where several countries are further North than many Canadian cities. To achieve the 50 nmol/L target level of circulating 25OHD, the IOM recom-

mended a modest increase in the recommended daily allowance for supplemental vitamin D to 600 IU/day. They also stated that although no adverse side-effects had been reported for doses of supplemental vitamin D up to 10 000 IU/day, a safe upper limit of 4000 IU/day was preferable. The IOM also pointed out that although clinical trials data did not currently support nonskeletal actions of vitamin D as a robust health outcome, there was nevertheless sufficient evidence to support more detailed studies in future.

The report was endorsed by many organizations such as the American Society for Bone and Mineral Research, and the cautious recommendations of the IOM have been supported in other reports(**65,60**). However, the support for the IOM proposals was not universal, and the report received a more hostile reception from many researchers in the world of vitamin D(**35,28,29,39**).Recommended dosage during the summer (UV index 3+): 20–40 IU/kg/day (1400–2800 IU/day for a 70kg / individual)(**62**).Recommended dosage during the winter (UV index less than 3): 40–80 IU/kg/day (2800–5600 IU/day for a 70kg / individual)(**62**).Year round dosage (depending on how far from the equator you live): 30–60 IU/kg/day (2100–4200 IU/day for a 70kg / individual)(**62**).The recommended daily dose (since 2005) of vitamin D for Bulgaria is: from age 19–30 years- 200 IU per day; 31–50 years- 200 IU per day; 51–70 years- men/women- 400/600 IU per day; over 71 years- 600 IU per day; pregnant/breast-feeding women- 200 IU/day.

INTRO, STRUCTURE AND PHARMACOKINETICS

Ingested Vitamin D can come in multiple forms, of which the most bioavailable is Vitamin D3, otherwise known as cholecalciferol. In the liver, cholecalciferol is turned into 25-hydroxycholecalciferol via the enzyme cholecalciferol 25-hydroxylase and then sent out to the kidneys to get hydroxylated into 1,25-dihydroxycalciferol (otherwise known as Calcitriol) which is considered the active form of Vitamin D.Vitamin D is potentially synergistic with Vitamin K supplementation as the two share many mechanisms of action in the cardiovascular and bone metabolism systems(**46**).

SERUM EFFECTS OF CALCITRIOL

Calcitriol can increase blood levels of calcium (vicariously through the parathyroid) by multiple mechanisms including:

- Increasing calcium uptake from the gut via Vitamin-D dependent calcium regulating protein(**44**)
- Increasing calcium release from bone mass
- Decreasing urinary excretion of calcium

WHAT LEVELS ARE OPTIMAL ?

Optimal levels for bone health begin at 75 nmol/L in older individuals(**76**).For many health endpoints (lower-extremity function, dental health, and risk of falls, fractures, and colorectal cancer) the benefits begin at serum levels of approximately 75 nmol/L, with the optimal range possibly being somewhere between 90 to 100 nmol/L(**6**).Serum parathyroid hormone levels are inversely associated with Vitamin D until Vitamin D levels reach between 75 and 100 nmol/L, meaning serum levels below 75 nmol/L might indicate deficient levels of Vitamin D(**39**)People with mean serum levels of 86.5 nmol/L had 65% better absorption of calcium than people with mean serum levels of 50 nmol/L(**36**).For colorectal cancer outcomes, people with serum levels of 82.5 nmol/L or greater had a 50% lower risk of developing cancer than those with a serum level below 30 nmol/L(**26**).

SERUM LEVELS OF VITAMIN D – HEALTH AND DISEASES

- Deficit of Vitamin D at ≤ 20 ng/ml (50 nmol/L).
- Slight Vitamin D deficiency from 21–29 ng/ml (52.5–72.5nmol/L).
- Normal „Ideal“ blood level of Vitamin D from 35 –40 ng/ml (87.5–100 nmol/L).

- Clinical signs of Vitamin D intoxication at ≥ 88 ng/ml (≥ 220 nmol/L).

HOW COMMON IS DEFICIENCY ?

In one study in the US 3% of the population had serum Vitamin D levels below 20 nmol/L (clinical deficiency), 29% of the population had levels below 50 nmol/L (insufficiency), and 79% of people had serum levels below 80 nmol/L(**12**). This indicates the majority of the US does not have Vitamin D levels in the optimal range.From 1988 to 2004 deficiency and insufficiency of Vitamin D has become more common, with levels below 75 nmol/L increasing from 55% to 77% of the population. Lower Vitamin D levels were even more common in non-Hispanic blacks(**26**).In subjects tested in Boston, serum Vitamin D levels were below 50 nmol/L in 11% of the subjects at the end of the summer, and 30% of subjects at the end of the winter(**67**).This illustrates that not only is their a seasonal variance in Vitamin D status in northern climates, but clinical insufficiency is quite common. There was also a variance in different age groups, with insufficiency being less common in people that were 50+. Boston has a latitude of 42 degrees N.

Britans also often suffer from inadequate levels of Vitamin D during the year. In the summer and fall 3.2% of people had serum levels below 25 nmol/L, 15.4% below 40 nmol/L, and 60.9% below 75 nmol/L. During the winter Vitamin D deficiency was even more common with 15.5% of people having levels below 25 nmol/L, 46.6% below 40 nmol/L, and 87.1% of people having levels below 75 nmol/L in the winter(**41**).This means that less than 15% of Britons had optimal Vitamin D status during the winter months. London has a latitude of 51 degrees N.In Estonia deficiency was also very common, especially during the winter. During the winter 8% of people had serum levels below 25 nmol/L, while 73% of them had serum levels below 50 nmol/L(**48**).Estonia has a latitude of 59 degrees N.Vitamin D deficiency can even be common in sun rich environment. This was the case in one study conducted in Isfahan City, Iran. 26.9% of the population had serum Vitamin D levels below 25 nmol/L, 50.8% below 50 nmol/L, and 70.4% below 75 nmol/L. Deficiency was more common in women and younger people, especially during the winter(**40**).These findings might in part be explained by the clothing that is commonly worn by women when they are outdoors in much of the Middle East. Isfahan City has a latitude of 32 degrees N.In one study conducted in Southern Florida deficiency was also fairly common. In winter approximately 38% of men and 40% of women had serum levels below 50 nmol/L(**50**). Miami has a latitude of 25 degrees N.Seasonal variation and latitude might not be the only variables that account for the difference in Vitamin D status. In one study in Australia seasonal variance and latitude each accounted for less than 1/5th of variance in serum Vitamin D(**71**). Deficiency is extremely common in medical inpatients, with 22% of patients having serum levels below 20 nmol/L and 57% having levels below 37.5 nmol/L in one study(**68**).

HOW MUCH DO WE NEED ?

Evidence suggests that as much as 10,000 IU/daily may be required to reach similar serum concentrations of Vitamin D as populations in sun-rich environments. Toxicity has occasionally been observed at 20,000 IU/daily after prolonged supplementation, and also in one individual receiving 300,000 IU/monthly.Up to 10,000 IU/daily can be produced from full body sun exposure when the UV index of the sun is greater than 3. This suggests that 10,000 IU/daily is the physiological limit on how much the body can adequately handle(**74**).Evidence suggests that adult males can readily utilize 3000–5000 IU of Vitamin D daily when it is supplemented(**37**).Approximately 1000 IU/d is required for 50% of the population to reach serum levels of at least 75 nmol/L(**6**).Approximately 1700 IU/d is required for 95% of the population to reach serum levels of at least 75 nmol/L(**75**).

VITAMIN D IS LISTED IN MICROGRAMS, AND THE RELATIONSHIP IS AS FOLLOWS:

- 2.5 mcg (micrograms) = 100 IU.
- 5 mcg = 200 IU.
- 10 mcg = 400 IU.
- 15 mcg = 600 IU.
- 20 mcg = 800 IU.

The following examples include:

- 100 IU (2.5 mcg) per day increases vitamin D blood levels 1 ng/ml (2.5 nmol/L).
- 200 IU (5 mcg) per day increases vitamin D blood levels 2 ng/ml (5 nmol/L).
- 400 IU (10 mcg) per day increases vitamin D blood levels 4 ng/ml (10 nmol/L).
- 500 IU (12.5 mcg) per day increases vitamin D blood levels 5 ng/ml (12.5 nmol/L).
- 800 IU (20 mcg) per day increases vitamin D blood levels 8 ng/ml (20 nmol/L).
- 1000 IU (25 mcg) per day increases vitamin D blood levels 10 ng/ml (25 nmol/L).
- 2000 IU (50 mcg) per day increases vitamin D blood levels 20 ng/ml (50 nmol/L).

MORTALITY

Low Vitamin D levels are associated with an increase in all-cause mortality(**52**).Vitamin D3, but not Vitamin D2 supplementation has been shown to decrease mortality in older adults(**8**).

HEART HEALTH (CARDIOVASCULAR DISEASE, ARTERIAL STIFFNESS, ATHEROSCLEROSIS)

Vitamin D levels have been associated with brachial flow-mediated dilation in Type 2 Diabetics. This indicates it plays an important role in heart function, especially in people with disease states**(82**).Those with insufficient Vitamin D levels are significantly more likely to develop heart disease than those who do not(**80**).Vitamin D status is associated with arterial stifness and vascular dysfunction in otherwise healthy humans(**54**). Vitamin D status might in part help explain the difference in risk of the development of peripheral arterial disease in darker populations (who are more likely to be Vitamin D deficient)(**61**). Supplementing 1000 IU/d of Vitamin D has been shown to reduce the risk of developing Cardiovascular Disease(**79**).Supplementing 3320 IU/d of Vitamin D helped improve several health markers of cardiovascular health during weight loss(**84**).

CANCER PREVENTION (BREAST, OVARIAN, COLORECTAL, PANCREATIC, SKIN)

Vitamin D supplementation has been shown to prevent the incidence of colon, prostate, breast, and ovarian cancer(**21**).Vitamin D levels have been inversely associated with BMI in cancer patients. This might be an indicator that nuritional requirements of Vitamin D may be increased for larger individuals(**72**).Vitamin D deficiency is common among women with breast cancer and supplementation is required to reach adequate levels. There was an inverse correlation found between severity of breast cancer and Vitamin D levels. 50,000 IU/week was more effective than 1000 IU/d in helping women to reach adequate levels(**56**).Women with breast cancer supplementing 400 IU/d of Vitamin D failed to reach adequate Vitamin D levels(**17**).Women supplementing with 2000 IU/d of Vitamin D may see upto a 50% reduction in the incidence of breast cancer(**21**).1000–2000 IU daily of Vitamin D prevents the incidence of colorectal cancer by up to 50%(**26**).Doses as low as 600 IU/d lower the risk of pancreatic cancer(**64**). UVB irradiation (which produces Vitamin D) is associated with a decreased risk of developing ovarian cancer in women(**22**).A Vitamin D receptor in the skin is responsible for repressing tumor formation in the skin(**23**).

EFFECTS ON LUNG FUNCTION (ASTHMA, UPPER RESPIRATORY TRACT INFECTION IMMUNITY,TUBERCULOSIS)

Vitamin D Levels have been inversely associated with upper respiratory tract infections, this relationship might be more important for those with respiratory tract diseases such as asthma(**25**). Low levels of Vitamin D are associated with more severe symptoms of asthma in children(**30**).Children taking 1200 IU of Vitamin D daily were 40%

less likely to get the flu during the winter, and the ones with asthma were also much less likely to suffer from asthma attacks(**68**).Post menopausal African women taking 800 IU daily for 3 years were 3x less likely to get the flu than those who didn't. Those taking 800 IU daily for the first 2 years and then 2000 IU daily for the next year were 26x less likely to get the flu. This means supplementing with Vitamin D helps prevent the flu(**1**).Lower Vitamin D levels are associated with an associated with a higher risk of active tuberculosis(**56**).

EFFECT ON INSULIN SENSITIVITY/ RESISTANCE & METABOLIC SYNDROME

Vitamin D levels have been inversely correlated with insulin resistance in non-diabetic adults(**51**).Vitamin D levels were inversely associated with serum levels of insulin in adolescents in the United States. People with a serum level of 75 nmol/L or more had approximately 24% lower levels of insulin on average than those with lower Vitamin D levels(**20**).Vitamin D levels have an inverse correlation with insulin resistance in both obese and non-obese children(**45**).During a glucose tolerance test, subjects who were considered to have insufficient levels of Vitamin D (50 nmol/L or less) were more likely to be insulin resistant and have beta cell dysfunction than those who had higher levels of serum Vitamin D(**16**).Supplementation of Vitamin D has been found to improve insulin sensitivity in people who were found to be deficient in Vitamin D, and improve their tolerance to a glucose tolerance test(**55**).Vitamin D3 deficiency may at least partly contribute to the impairment of insulin secretion and probably of insulin action.Vitamin D3 supplementation could be an element in the complex treatment of type 2 diabetes mellitus during the winter(**11**).

EFFECT ON HORMONES (TESTOSTERONE/ ESTROGEN)

Vitamin D receptors are expressed in the male reproductive system, and Vitamin D might play an important role in reproduction(**9**).Vitamin D is required to maintain adequate levels of estrogen in both males and females, by maintaining aromatase levels(**47**).Serum Vitamin D levels are associated with Androgenic metabolites including Testosterone, and testosterone levels are highest in the summer and lowest in the winter(**81**).Vitamin D deficiency is associated with decreased sperm motility(**42**).Supplementing 3332 IU of Vitamin D daily for a year increased levels of total, active and bound testosterone in healthy, overweight men(**58**).Joint pain when taking aromatase inhibitors is associated with low levels of Vitamin D(**78**).Bringing up serum concentrations to levels of 100 nmol/L helps prevent arthralgia (joint pain) associated with prescription aromatase inhibitors(**59**).

EFFECT ON STRENGTH / MUSCLE / FALLS AND / OR ATHLETIC PERFORMANCE

Vitamin D deficiency is associated with high levels of fat in muscle tissue, independent of several other factors(**23**).Vitamin D Receptors (VDR) are found in skeletal muscle cells(**3**).Adequate amounts of Vitamin D increases the number of VDR in muscle cells(**15**).VDR Expression in muscle cells also decreases with age(**6**).Vitamin D deficiency appears to contribute to the age-related loss of muscle strength in the elderly(**3**). Vitamin D deficiency also appears in part to cause loss of muscle mass in elderly adults(**77**). Attenuating a Vitamin D deficiency increases the amount of type II muscle fibers (fast-twitch) in the elderly who have suffered from a stroke, and decreases the risk of falling related injuries(**63**). Supplemental Vitamin D helped improve performance on a 2 minute walking test in elderly Vitamin D deficient women(**73**).Supplementation of Vitamin D to correct a deficiency may improve Athletic performance in athletes. A serum Vitamin D level of 125 nmol/L may be required to do so(**14**).Low Vitamin D status has been associated with an increased risk of illness amongst athletes, and athletes might benefit from supplementation(**32**).NFL players who suffered from injuries were more likely to have insufficient levels of Vitamin D(**49**).High serum

levels of Vitamin D are correlated to a reduced risk of stress fractures, which would likely result in a benefit for athletes(**13**).Meta-analysis show that Vitamin D supplementation appears to reduce the risk of falls among ambulatory or institutionalized older individuals with stable health by more than 20%9(**5**).

PREGNANCY AND LACTATION

Vitamin D deficiency is very common in pregnant women, and it is hypothesized Vitamin D requirements during pregnancy are increased relative to normal(**31**).Vitamin D deficiency or insufficiency affected 97% of African-Americans, 81% of Hispanics, and 67% of Caucasians in one trial(**43**).Vitamin D deficiency during pregnancy may even be common in sun rich environments. In one study women in South Carolina (Latitude of 32N) were often found to have insufficient levels of Vitamin D. Of the women examined 48% had a Vitamin D deficiency, and 48% had levels below 50 nmol/L, with only 15% having levels greater than 80 nmol/L(**33**). Clinical deficiency is common in pregnancy, especially in non-western women(**70**).Serum Vitamin D levels in women have been linked to the development of Type 1 Diabetes in offspring. Women with Vitamin D deficiency were more than two times more likely to have their children develop Type 1 Diabetes than women with adequate levels(**66**).Low Vitamin D levels during pregnancy have been associated with an increased of having to undergo Caesarean Section. Women with serum levels of 37.5 nmol/L or more were almost 4x less likely to require a caesarean section(**53**).Maternal Vitamin D intake during pregnancy has been inversely associated with the development of asthma and allergic rhinitis in 5 year old children(**18**).Vitamin D deficiency has been associated with the development of Bacterial vaginosis during the first trimester of pregnancy. 57% of women with Vitamin D levels below 20 nmol/L had Bacterial vaginosis, while only 23% of women with Vitamin D levels above 80 nmol/L did(**10**).A one time dose of 200,000 IU or a daily dose of 800 IU/d during pregnancy was often not enough for women and their offspring to reach sufficient levels of serum Vitamin D(**83**).Supplementation of 4000 IU/day of Vitamin D during pregnancy was better than 2000 IU/d and 400 IU/d for raising serum Vitamin D levels to adequate levels. There were no adverse effects reported at supplementation of 4000 IU/d and it was concluded that 4000IU/d should be supplemented during pregnancy(**39**).Supplementation of 1000 IU/d or less is often not enough to correct Vitamin D deficiency and insufficiency during pregnancy. Adequate serum Vitamin D concentrations have been reached after supplementing 4000 IU/d and have been well tolerated (no adverse effects). Vitamin D supplementation may also be very important during lactation as well as during pregnancy(**19**).

BONE HEALTH AND OSTEOPOROSIS

The recommended daily dose of vitamin D for prevention and treatment of osteoporosis (Bulgarian Society of Endocrinology-2005) from all sources („all sources" implies the accepted food and food supplements) is:

A) Men and women under 65 years of age- 400 IU (10 micrograms) daily
B) Men and women over 65 years of age- 800 IU (20 micrograms) daily

The recommended daily dose of calcium is 1000 mg.

CONCLUSSIONS

In the last five years there is a significant change in our understanding of the health advantages of vitamin D. The most interesting aspect is the non-skeletal effect of vitamin D. The impaired vitamin D homeostasis is quite common all over the world. Different studies connect vitamin D deficiency with some chronic health problems, including autoimmune and cardiovascular diseases, arterial hypertension, cancer, etc. Numerous in vitro studies in animal models support the undisputable roles of vitamin D for human health, the most significant of which are

immunomodulating and anticancerogenous effects, depending as it seems on the local activation of vitamin D. The conclusion is that most of these so to say non-classic effects of vitamin D are independent of the known effects of vitamin D and for that reason are more sensitive to shifts from the normal range of vitamin D.

It is not accepted to let doctors just guess the level of blood cholesterol or blood sugar and prescribe medications. Doctors have access to precise blood glucose and cholesterol testing, which enables adequate treatment. So the same should apply for vitamin D.

So it is about time the NHIF started covering for the routine testing of vitamin D blood levels as it does in other cases of endocrine pathology. The recommended daily dose of vitamin D will be individualized (according to age, pregnancy, lactation, etc.) with the aim to achieve normal levels of 25 OH vitamin D (35–40 ng/ml or 87,5–100 nmol/l), that is „hormonal remission".

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Risk evaluation of thrombophilic diathesis in breast cancer patients with localized and metastatic disease

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Оценка на риска от тромбофилна диатеза при пациенти с карцином на млечната жлеза с локализирано и метастазирало заболяване

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РЕЗЮМЕ

Онкологичните пациенти изявяват повишена склонност към тромбофилна диатеза в хода на своето заболяване. Венозният тромбоемболизъм и съпътстващите фатални усложнения са една от най-честите причини за болестност и смъртност при тези пациенти.

ЦЕЛ НА ПРОУЧВАНЕТО

Да се оцени риска от тромбофилна диатеза при пациенти с карцином на млечната жлеза с локализирано и метастазирало заболяване.

МАТЕРИАЛ И МЕТОДИ

Ретроспективно са анализирани 92 пациенти с карцином на млечната жлеза, лекувани в Клиника по Онкология и Хематоло-

ABSTRACT

Cancer patients are prone to heightened propensity for thromboembolic episodes (TEE) during the natural history of their disease. Venous thromboembolism (VTE) and its fatal complications account for increased morbidity and mortality.

AIM OF THE STUDY

To evaluate the risk of VTE in breast cancer patients with localized and metastatic disease by applying a recently validated novel VTE score model for cancer patients.

MATERIAL AND METHODS

Retrospective analysis of the medical charts of 92 women treated at the Clinic of Oncology and

гия, УМБАЛ „Св. Георги“ ЕАД, за периода от 2009г. до първите 6 мес. На 2012г. Рискът от тромбофилна диатеза е оценен на базата на съществуващ общодостъпен скор, използващ стойности на тромбоцити, хемоглобин и левкоцити преди стартиране на системно лечение, локализация на туморния процес и индекс на телесната маса.

РЕЗУЛТАТИ

Общо 67 пациенти са оценени с нисък рисков профил на базата на използвания скор, 24 – с междинен риск и един пациент с висок риск. Пациентите с нисък риск съставляват 75 % (n=36) от групата с локализирано заболяване и 70.5 % (n=31) от тези с метастазирало заболяване. Пациентите с междинен риск представляват 25 % (12) от тези с локализирано заболяване и 27.3 % (12) от групата с далечни метастази. Пациентът с висок риск е с метастазирало заболяване. Не се установява статистически значима разлика в рисковия скор между двете групи пациенти (p=0.585, $\chi 2$=0.548).

ЗАКЛЮЧЕНИЕ

С цел да се идентифицират пациентите с повишен риск от венозен тромбоемболизъм е необходимо те да бъдат активно мониторирани чрез специфични хемостазни параметри. Феноменът на тромбофилна диатеза при онкологичните пациенти оправдава създаването на регистър на тромбоемболичните инциденти сред тази пациентска група.

Hematology, University Multiprofile Hospital „Sveti Georgi“, Plovdiv from 2009 to the first 6 months of 2012. VTE score was calculated on the basis of the validated VTE score proposed by Khorana et al. Statistical analysis was performed in order to assess differences in VTE risk score among patients with localized and metastatic disease.

RESULTS

A total of 67 patients had low risk for VTE, 24 – intermediate risk and 1 patient was identified at high risk for VTE. Low risk patients comprised 75 % (n=36) of the patients with localized disease and 70.5 % (n=31) of the patients with metastatic disease. Intermediate risk patients accounted for 25 % (12) in the localized patients group and 27.3 % (12) in the group with metastatic spread. High risk patient had advanced disease. No statistically significant difference was detected (p=0.585, $\chi 2$=0.548) when testing for differences in VTE score between the two groups.

CONCLUSION

In order to identify those cancer patients at risk for VTE, active surveillance of treated population by using specific hemostatic biomarkers is necessary. The development of a VTE registry for cancer patients is justified.

INTRODUCTION

Cancer patients are prone to heightened propensity for thromboembolic episodes (TEE) during the natural history of their disease. The state of hypercoagulability in cancer is associated with tumor growth itself and is considered an early sign of malignancy. Understanding the link between thrombosis and cancer is of critical importance to the management of cancer patients, because thromboembolic disease (TED) and its complications may negatively impact patient outcome (4, 10). The application of risk-assessment tools for VTE in clinical practice can help aid in identifying cancer patients at high risk who could benefit from anticoagulant prophylaxis.

The activation of blood coagulation in cancer was observed back in the 19th century by Prof. Trousseau who reported high incidence of superficial migratory thrombophlebitis at uncommon sites in patients with gastric carcinoma known as Trousseau syndrome (15). The association of TED and cancer has since been validated both in studies demonstrating a high rate of idiopathic and unprovoked venous thromboembolic events (VTE) preceding the diagnosis of cancer and an increased incidence of VTE in patients suffering from cancer (3,11,13,16). The clinical occurrence of VTE in cancer patients confers reduced survival. This can be attributed to the increased morbidity and mortality due to the development of VTE and its fatal complications. However, it is considered that thrombophilic diathesis in malignancy reflects more aggressive disease and facilitates cancer progression related processes such as tumor growth and angiogenesis. As cancer can trigger blood coagulation by tumor-specific prothrombotic properties such as procoagulant production, secretion of proinflammatory cytokines, endothelial damage and direct cell-to-cell interactions, it is anticipated that patients with metastatic disease would be at higher risk for developing thromboembolic events (1). Furthermore, in 40% of the cancer patients with concurrent DVT at presentation there is already evidence of distant disease (8). Therefore the aim of our study was to evaluate the risk of VTE in breast cancer patients with localized and metastatic disease with the help of a recently validated novel VTE score model predictive for chemotherapy-associated thrombosis.

MATERIAL AND METHODS

The study population comprised 92 women treated at the Clinic of Oncology and Hematology, University Multiprofile Hospital „Sveti Georgi", Plovdiv from 2009 to the first 6 months of 2012, split into 48 patients with localized breast cancer and 44 patients with metastatic disease.

Patients' medical charts were retrospectively reviewed and analyzed. Patients' characteristics and baseline laboratory values were obtained. Data on previous history of TEE was obtained, as well as any clinically significant TEEs during the course of treatment were recorded. The risk for VTE was assessed by using a novel clinical risk score that has been recently developed and validated by Khorana et. al (7). The proposed predictive risk model combines five easily available clinical and laboratory parameters in order to calculate the risk for developing VTE upon initiating systemic polychemotherapy. It utilizes the parameters: site of cancer, prechemotherapy platelet counts, prechemotherapy leukocyte counts, hemoglobin level and body mass index (Table 1).

*Table 1. Predictive model for chemotherapy-associated VTE (7). *Risk score: high risk > 3; intermediate risk = 1–2; low risk = 0.*

Patient characteristics	Risk score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350 x 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11 x 10^9/L	1
BMI 35 kg/m^2 or more	1

Based on the site of cancer patients are assigned the highest points if they qualify as at high risk by having stomach or pancreatic cancer. Breast, colorectal, head and neck cancer and any other sites of cancer except for those comprising the very high risk and the high risk groups are assigned zero points. One point is assigned if patients have each of the following: prechemotherapy platelet count 350 x 10^9/L or more, prechemotherapy leukocyte count greater than 11 x 10^9/L, hemoglobin level less than 100 g/l or use of erythropoiesis stimulating agents, body mass index 35 kg/m^2 or more.

Risk score categorizes cancer patients into three groups based on the sum of separate parameters: low = 0, intermediate = 1–2 and high > 3. In our study population the VTE score was calculated for each patient individually according to the model. Differences within the VTE score between the two groups were tested with the Mann-Whitney U test and Pearson's chi-squared test. Normality of distribution was tested with the Kolmogorov-Smirnov test. Statistical analysis was performed on SPSS v.20 for Windows (SPSS, Chicago, IL, USA).

RESULTS

In the group with localized breast cancer all cases had negative history for TEE. Among the patients with metastatic disease 2 patients (4.5%) had positive history for TEE. One patient suffered myocardial infarction two years after diagnosis of breast cancer was established. Second patient suffered pulmonary embolism four years prior to diagnosis of breast cancer and an ischemic stroke four years after diagnosis. Patient characteristics in relation to the scoring variables are presented in Table. 2.

Table 2. Characteristics of patients in the localized and metastatic disease groups

Patient characteristics	Localized, no. (%)	Metastatic, no. (%)	p
Baseline parameters			
Prechemotherapy platelet count 350 x 10^9/L or more	9 (9.8)	12 (13.0)	.09
Prechemotherapy leukocyte count more than 11 x 10^9/L	2 (2.8)	2 (2.8)	.23
Hemoglobin level less than 100 g/L	3 (3.5)	4 (4.3)	.51
BMI 35 kg/m2 or more	0 (0)	0 (0)	
Recorded VTE events after chemotherapy initiation	4 (4.3)	4 (4.3)	.319

Within the studied patient population a total of 67 patients had low risk for VTE, 24 had intermediate risk and 1 patient was identified at high risk for VTE (Figure 1). Low risk patients comprised 75 % (n=36) of the patients with localized disease and 70.5 % (n=31) of the patients with metastatic disease. Intermediate risk patients accounted for 25 % (12) in the localized patients group and 27.3 % (12) in the group with metastatic spread. The only patient identified at high risk according to the score model had advanced disease (Figure 2).

Figure 1.
Distribution of patients according to VTE risk score.

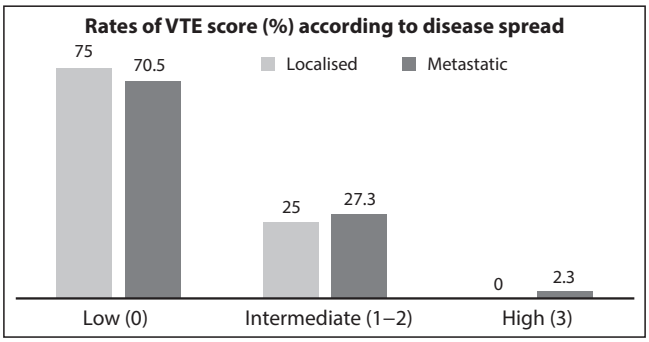
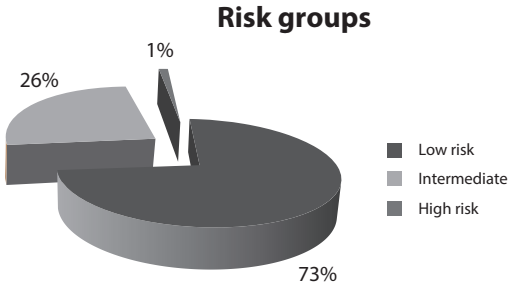


Figure 2.
Rates of VTE score according to disease spread.



During the course of systemic polychemotherapy a total of 8 (8.6 %) cases of symptomatic thrombotic events were recorded, split into 4 cases for each group. Six patients had DVT/extremity thrombophlebitis, one suffered an ischemic stroke and one – pulmonary embolism. TEE occurrence did not impose cessation of systemic treatment or postponement of the consecutive cycle. Of all registered symptomatic TEEs one patient had intermediate risk profile and the other seven – low risk.

When testing for differences in VTE score between the two groups, assessed on the basis of the proposed risk model, using Mann-Whitney U test and Pearson's chi-squared test, after

testing with Kolmogorov-Smirnov for normality of distribution, no statistically significant difference was detected (p=0.585, χ^2=0.548). Both studied groups exhibit equal distribution of the VTE risk score.

DISCUSSION

From the classic viewpoint of the Virchow's triad cancer disrupts the hemostatic balance by causing alterations in all three of its components. Tumor-specific factors contributing to the prothrombotic state of malignancy include overexpression of proinflmmatory and adhesion molecules by endothelial cells, impaired blood flow by growing tumor masses, hyperviscosity and constitutively activated coagulation by secreted from tumor cells procoagulant substances (6). Moreover, therapy-related factors impose additional risk. Cytostatica treatment, use of antiangiogenic agents, placement of intravenous devices contribute to the development of thrombophilic diathesis. Among the cancer population specific sites of cancer and histology are predisposing to the occurrence of VTE. Highest rates of VTE are observed in patients with pancreatic, stomach, lung cancer with the histology of adenocarcinoma (6). The risk of developing malignancy increases up to 12 fold in 6–12 months after an episode of idiopathic DVT. It is anticipated that 7.5% of the patients will be diagnosed with cancer in the next 2–3 years after VTE episode (1,5). In a prospective study the risk of being diagnosed with cancer in the first year after idiopathic thrombosis is 4–7 fold higher compared to patients with VTE secondary to known causes and this risk was 10-fold greater in the case of idiopathic recurrent VTE (13). Risk analysis using Medicare database demonstrated that patients with simultaneous DVT/PE and malignancy are at 3-fold higher risk of recurrent TED and death than patients with DVT/PE without malignancy (9). It has also been noted that the presence of VTE is a sign of higher disease aggressiveness. A prospective study by Sorensen et al. demonstrated poorer prognosis and an increased risk for distant metastasis in cancer patients in whom the diagnosis was either set at the time of the thrombotic event or one year thereafter (14).

This data confirms the need for establishing and applying in the clinical practice risk-assessment tools for identifying those cancer patients who are at risk for VTE and who would eventually benefit from anticoagulant prophylaxis. The novel clinical risk score for evaluating the VTE risk in cancer patients is an easily applicable risk-assessment tool for cancer-associated VTE in the clinical practice (7). The external prospective validation of this predictive model by the Vienna CATS study revealed the 6-month cumulative probability of developing VTE to be 1.5% (score 0), 3.8% (score 1), 9.4% (score 2) and 17.7 % (score 3) (2).

In our study population the risk for developing VTE was equal for both groups regardless of disease spread. That could be attributed to the site of cancer on one hand, since breast cancer is considered primarily low risk for the development of VTE. On the other hand, patients in the group with distant metastases might be experiencing effects of both hematologic toxicity after previous chemotherapy and marrow infiltration due to metastases. This could account for suppressed cellular production from bone marrow and thus altering the VTE score by seemingly within normal ranges hematologic parameters. Secondarily, one could argue that procoagulant activity is proportional to growth activity the same way as cytostatics cell kill is proportional to cell growth. Since breast cancer exhibits a Gompertzian model of growth (12), greater tumor load in cases of metastatic disease could reflect a functionally stable cell population that exhibits its inherent procoagulant properties to e lesser extent.

CONCLUSION

Hemostatic system and its components is a dynamic system, which would require the use of specific biomarkers for monitoring its state of activation and the risk for thromboembolism. In order to identify those cancer patients at risk for VTE,

active surveillance of treated population by using specific hemostatic biomarkers is necessary. Aiming at the „live“ data on VTE incidence, prevalence and need for prophylaxis in our population the development of a VTE registry is justified.

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Contemporary criteria of pathomorphological diagnosis of gastrointestinal stromal tumors (GIST) (Analysis of 76 personal cases)

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Съвременни критерии за патоморфологичната диагностика на гастроинтестиналните стромални тумори /ГИСТ//Анализ на 76 собствени случаи/

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РЕЗЮМЕ

ГИСТ са самостоятелна туморна група, обособени в последното десетилетие в резултат на установяване на произхода им от клетките на Кахал и откриването на свръхекспресията на мутирал КИТ рецептор като основен фактор в канцерогенезата.

ЦЕЛ на настоящото проучване е анализ на резултатите от комплексното морфологично изследване на ГИСТ, диагностицирани в отделението по клинична патология в Пирогов с акцент върху значението на имунохистохимичните и прогностични критерии. Предлага се алгоритъм за хистопатологичен протокол. Общият брой на изследваните случаи е 86 за период от 11 години, от които 76 са на пациенти от хирургичните клиники на Пирогов. Резултатите потвърждават високия процент на ГИСТ сред мезенхимните тумори, което съвпада с литературните данни. Наблюдава се значително разнообразие с определено доминиране на вретеновидно-клетъчния вариант. Имунохистохи-

ABSTRACT

GIST are a separate oncologic group, determined in the last decade, by the identification of their origin from the Cajal's cells and a mutation of the KIT-receptor, which is a main factor in their carcinogenesis.

The aim of this study is the analysis of the results of a complex morphological research on GIST , diagnosed at the ward of „Clinical Pathology“ at Pirogov Hospital, emphasizing the significance of the immunohistochemical and prognostic criteria. We suggest an algorithm of a pathohistological protocol. The total number of the reviewed cases is 86, for a period of eleven years. 76 of these cases are from the surgical clinics in Pirogov. The results confirm the high percent of GIST among the mesenchymal tumors of the gastrointestinal tract, which coincides with the available official data. The spindle-cell type is the dominating histological variant among the various observed. CD-117 expression is of greatest significance for diagnosing GIST, from the different immunohistochemical tests.

мичното изследване и по-точно експресията на СД-117 е от първостепенно значение за диагностиката на ГИСТ, който е най-важния биомаркер свързан със соматичната мутация на КИТ гена, присъстващ в около 80% от ГИСТ туморите и позволяващ точна диференциална диагноза. Установяването на свръхекспресия на мутирали форми на КИТ рецептора на тирозин-киназата е в основата на канцерогенезата им, като с атакуването на тази мутация с тирозин-киназни инхибитори се постави началото на успешната молекулна таргетна терапия

It is the most important biomarker, connected to the somatic mutation of the KIT-gene, present in 80% of GIST, allowing accurate differential diagnosis. The identification of over-expression of mutated forms of the KIT receptor of the tyrosine-kinase is the basis of their carcinogenesis. This has given ground for the successful initiation of molecular target-therapy, attacking this mutation by tyrosine-kinase inhibitors.

Key words: gastrointestinal stromal tumors, immunohistochemistry, CD-117, tyrosin-kinase mutations

INTRODUCTION

GIST are classified as a separate oncologic group in the last decade with identified histogenesis from the interstitial Cajal's cells and an oncogenic mutation of the KIT-receptor , which is a main factor in their carcinogenesis. The implementation of tyrosin-kinase inhibitors set the start of a successful molecular target-therapy.

There are several unresolved problems associated with the diagnostic process, genetic status and treatment of GIST, despite the progress in their study. Recently there was implemented a new plan of assessment of the risk of recurrence, which determines the treatment. The pathohistological test plays a key-role in proving the expression of CD117 and several predictive and prognostic factors.

The aim of this study is the analysis of the results of a complex morphological research on GIST , diagnosed at the „Clinical Pathology" ward at Pirogov Hospital, emphasizing the significance of the immunohistochemical and prognostic criteria.

MATERIALS AND METHODS:

The total number of the reviewed tumors is 86. There have been included 52 non-epithelial stromal tumors of the gastrointestinal tract, operated at the surgical clinics of Pirogov over an eleven-year period /2001–2011/ and 34 consulted cases after year 2005. All of these have been submitted to routine histological and standard immunohistochemical tests on deparaffined sections. The following antibodies, produced by Dako, have been used : CD117, Desmin, CD 34, S-100 protein.

RESULTS

The morphological examination of the tumors of the gastrointestinal tract, including the reevaluation of the patients operated after 2004yr. showed 76 cases of GIST /88,37%/ and 10 cases of other mesenchymal tumors.

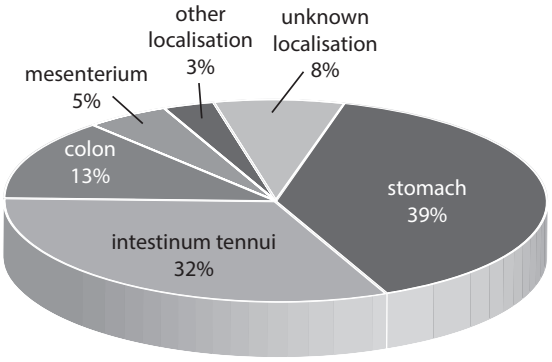
Table 1

MESENHYMAL TUMORS OF GIT before 2004 yrs and after 2005 yrs			
Number / Period	Total mesenhymal	GIST	Other mesenhymal tumors
2000–2004 г.	27	23 revised	4
2005–2011 г.	59	53	6
TOTAL:	86	76 /88.37%/	10 /11.62%/

Gender distribution – 42 women, 34 – men. Ratio – 1,24.Age distribution varies from 22 to 81 years of age, highest frequency being in the interval 58–62 years of age.

Location – The predominant location of GIST in the mentioned cases is in the stomach, followed by the small intestine.

Fig.1.
Localisation of the GIST



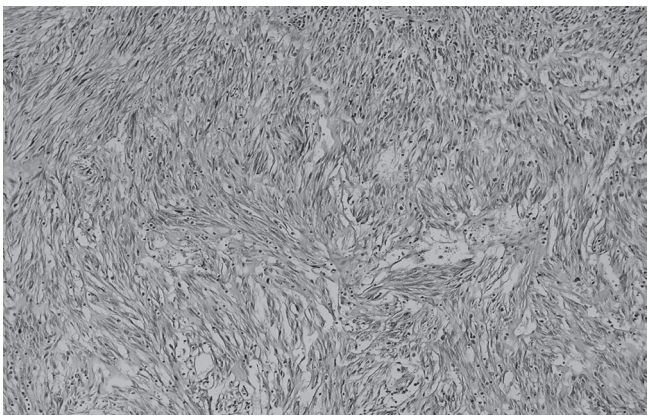
MACROSCOPIC APPEARANCE AND SIZE

These formations are well circumscribed, oval nodules, measuring from 2cm to 20cm, 5–10cm in average . The largest tumors are found in the stomach and the colon, with infiltration towards the serosa. In two of the cases, there were identified numerous tumors in the mesenterium, from 3cm to 8cm large. One of them is a late metastasis discovered 4,5years after a resection of the small intestine due to a tumor, diagnosed as leiomyosarcoma. In the second case – a tumor in the small intestine was discovered (d=3cm),after a histological diagnosis of GIST. It was surgically removed. In two other cases there were discovered GIST metastases in the liver : in the first case (woman, 34 yrs old), these metastases developed 9 years after an operation due to a 'leiomyoblastoma' of the stomach and are represented by numerous cystic formations on the CT-scan and myxomatous appearance according to the surgical protocol. In the second case, there were discovered many well defined nodules from 1 to 3cm in diameter with white colour and dense elastic consistence.Three of the tumors (two in the stomach and one in the colon) had a polypoid macroscopic appearance.

Microscopic characteristics : We have used the classical microscopic criteria for identifying the two main histological types – spindle cell and epitheloid, and the mixed type, which expresses the features of both.

The spindle cell type is the most frequent (57 cases). It is composed of elongated cells arranged in intermingled fascicles and it often forms palisades. The nuclei are oblong, contain dispersed chromatin and small nucleolei. The perinuclear vacuolization is very distinct, which can simulate the look of a liposarcoma. It is represented by a considerable variety in its structural and cellular content : the fascicles are short or long, whirl-like or fan-shaped.The stromal changes vary from hyalinized to myxoid stroma with or without inflammatory infiltration . A relatively distinct outlook of the spindle cell tumor is a combination of short fascicles in whirl-like structures (as in fibrohistiocytic tumors), the presence of palisades and vacuolization of the cells.

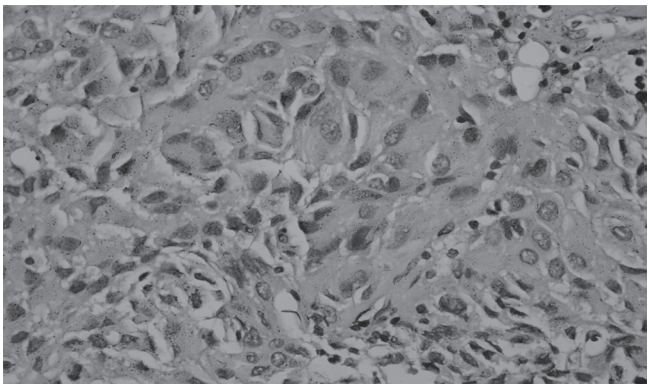
Fig.2.
Histological feature of the spindle variant).



The epitheloid variant consists of round, oval or polygonal cells with abundant eosinophilic cytoplasm, often forming 'cohesive' zones – tightly arranged cell groups. The nuclei are spheric, vesiculated, usually containing prominent nucleolei.

Mixed tumors – nine in total. There is a tumor of the small intestine, which is rare and unreported until now . It contains a mixed-cell population of spindle and epitheloid cells and forms whorle pattern similar to the meningothelial whorls.

Fig.3.
Histological feature of epitheloid variant) In our study there are only 3 typically epitheloid variants.



In the rest 8 cases, we examined the following atypical forms, single case each:

- with extensive pleomorphism, rich in giant tumor cells.
- stromal xantomatisation and inflammatory infiltration (stomach)
- hypocellular sclerosing, phenotypically like a solitary fibrous tumor.
- rich-cell sarcomatoid with high mitotic index
- with prominent stromal myxomatization
- with generalized cellular vacuolization
- with dominating palisade structures, without fascicular formation.
- with well expressed vascular component, suggesting of primary vascular tumor

In these cases we also include a tumor with evident neuronal differentiation, corresponding to Gastrointestinal Autonomic Neurogenic Tumor (GANT).

The immunohistochemical tests are positive for CD117 in 75 of all cases and its expression is a main criteria to diagnose them as GIST.

The immune reaction varies from strongly positive in nearly 100% of the tumor cells to weak in the cells' processes in about 50% of the cells.

On the basis of the immunohistochemical tests, we build our the differential diagnose as well. (Table 2: Results of immunohistochemical study of mesenhymal tumors of GIT)

Since it is necessary to evaluate the reliable prognostic and predictive factors in order to define the suitable treatment, we used the latest recommendations of the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO). According to them, the evaluation of the risk of malignant tumor behavior should be based on three factors : mitotic index, site and size of the tumor.

Fig. 4.
Positive Immunohisto-chemiall reaction for CD117 in spindle variant

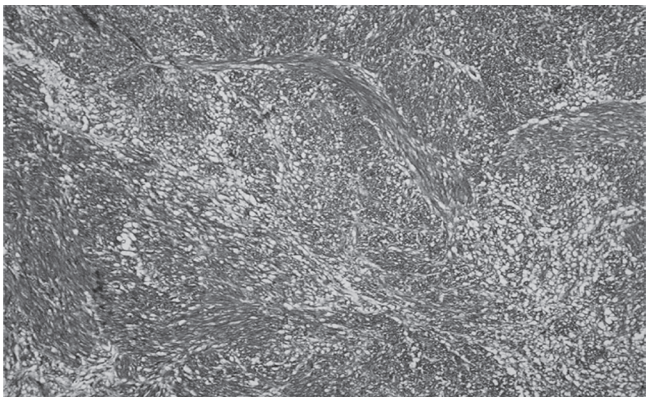


Table 2

RESULTS OF IMMUNOHISTOCHEMICAL STUDY OF MESENHYMAL TUMORS OF GIT

Methods Number	CD117 (c-KIT)	CD34	Desmin	S-100
GIST 76 cases	(+) 75	(+) 42 (55,3 %)	(+) 3 (3,9 %)	(+) 5 (6,5 %)
Leiomyosarcoma 4 cases	(–)	(+)	(+)	1 case (+)
Neurinoma 2 cases	(–)	(+)	(–)	(+)
Melanoma * 2 cases	(+)	(–)	(–)	(+)
Liposarcoma 2 cases	(–)	(–)	(–)	(+)

Having in mind the number of factors needed to define the evolution of GIST, which can not be assessed only upon the histological type, we suggest an standart pathomorphological protocol.(see applying). It should contain detailed macroscopic , microscopic and immunohistochemical characteristics, along with the appraisal of the risk of completely removed tumors.

Table 3.
Prognostic and predictive criterias of GIST).

Risk stratification of GIST,s					
Mytotic index	Size	SITE			
		Gastric	Jejunum/ ileum	Duodenum	Rectum
≤ 5 / 50 HPF	≤ 2 cm	no risk	no risk	no risk	no risk
	> 2 ≤ 5 cm	very low	Low	low	Low
	> 5 ≤ 10 cm	low	**interme-diate**	high	High
	> 10 cm	**interme-diate**	High		
> 5 / 50 HPF	≤ 2 cm	no risk	High	unknown	High
	> 2 ≤ 5 cm	**interme-diate**	High	high	High
	> 5 ≤ 10 cm	high	High	high	High
	> 10 cm	high	High		

DISCUSSION

Our results show extensive dominance of GIST among the mesenchymal tumors of the gastrointestinal tract and coincide with the available data for uniform distribution in gender, higher occurrence in adults and most common localization in the stomach.

Histologically GIST are quite diverse, but have two main types : spindle cell type (predominant) and epitheloid-cell. In the spindle cell variant there are significant structural differences, which correspond to the subtypes defined by M. Mietinnen et al. – sclerosing, palisade-vacuolized, hypercellular and sarcomatoid and some very rare types : with prominent myxoid stroma /5%/, signet-ring cell, with strong inflammatory reaction, with pronounced pleomorphism, with alveolar look, paraganglioma-like, carcinoid-like. We have also noticed a significant variety in our cases, some of which (sclerosing hypocellular, palisade-vacuolized and with prominent myxomatization) occurs rarely. The variability of the histological fenotype of GIST exiges these tumors to be included in differential diagnosis of many, almost all , mesenchymal tumor of gastrointestinal tract. The addition of GANT to GIST is motivated by their common immunohistochemical and genetic features with the conventional forms – they express KIT 117 protein and contain the same mutations (3).

The immunohistochemical testing of CD117 is of prime significance for the diagnostic process of GIST

It is the most important biomarker, linked to a somatic mutation in the KIT gene and proves GIST in about 95% (8,13,15,20). As a result of this about 80% of the gastrointestinal mesenchymal tumors were pre-classified as GIST. The retrospective reevaluation of our cases reassessed 76 of a total of 85 mesenchymal tumors of the gastrointestinal tract as GIST (89,1%). The immunohistochemical staining as a percent of the reactivity of the cells and intensity of the reaction varies significantly according to official data. In a major part of our cases the reaction is highly intensive and present in over 80% of the tumor cells. A weaker reaction is seen in hypocellular tumors, those with hyalinization or myxomatized stroma and in GANT. The most decisive factor is the presence of CD117, not the intensity of the reaction, because it has been proven that it has no effect on the sensitivity to tyrosine-kinase inhibitors.

Differential diagnoses is done mainly with the other 'mesenchymal' or 'stromal' tumors of the gastrointestinal tract, diagnosed before 1998yr., when it was proven that GIST are fundamentally different mostly due to the positive reaction for CD117. This reaction is extremely useful for the differentiation from the other mesenchymal tumors, which express characteristic antigens, except CD117. Some of these include : leiomyomas and leiomyosarcomas, neurinomas and malignant peripheral nerve sheath tumors(MPNST), abdominal fibromatosis, myofibroblastic tumors, solitary fibrous tumor, carcinosarcoma and anaplastic carcinoid, neuroendocrine tumors, synovial sarcoma, malignant mesothelioma.

IT IS WORTH CONSIDERING THE FOLLOWING WHEN TESTING TUMORS FOR CD117

- Around 5% are CD117 negative (17). The negative immune reaction for desmin, SMA

and S-100 protein and the positive reaction for CD34 with the relevant localization and histological type are good enough reasons to accept GIST as the correct diagnosis. It is recommended however to use other methods – for PDGFR, DOG-1 (Delete on GIST), PKC-teta and eventually genetic tests.

- Other malignant tumors besides GIST can also express CD117 – malignant melanoma, liposarcoma, germ cell tumors and others. A great role for the diagnosis of these tumors if the comparison of their histological type and the results of a wide panel of immunihistochemical tests, for eg. Melan A, HMB45 for malignant melanoma.

PROGNOSTIC AND PREDICTIVE FACTORS

Large scale multifactor studies have proven the prognostic and predictive significance of the site, size and mitotic rate of GIST. As a result, the previous scheme of NIH (8) was replaced by the newly accepted with a consensus and recommended by NCCN and ESMO,2007 (7,19). The role of several factors as histological type, rupture of the tumor, peritoneal or mucosal invasion, total resection, coagulation necrosis, DNA polyploidy status, expression of muscle or neuronal markers is being presently researched. It is admissible that the histological subtype and the progress of the tumors are related, but this has not been proven yet as a prognostic value.

The significance of the KIT mutations as prognostic factor is increasing, but is still contradictory (10). An opinion prevails, that the specific kind of mutation is more important than its localization. Other than that the predictive significance of the specific mutations is being emphasized(4,5,12,14). The present results prove that KIT mutations can be accepted as standard tests for GIST in the near future.

In conclusion, our modern knowledge of GIST allows us to succeed with the target therapy of this type of tumors. This success if permitted by the exact histological diagnosis and the evaluation of the predictive factors, which determine the optimal treatment.

APPLYING: PROPOSED REPORT OF PATHOMORPHOLOGIC RESULT

1. Passport and relevant clinical data, including results of imagining diagnostics /localization and size of the tumor, spreading, metastases/.
2. Macroscopic description of the:
   - resected material
   - tumor – size, form, location, spreading to the mucosa, serosa, restriction?, relation to adjacent organs.
   - additional materials – lymph nodes, suspicious for metastatic.
3. Microscopic description :
   - Cellular and architectural characterisation.
   - Defining the histological type of the tumor.
   - Number of mitoses in 50 HPF (high power fields).
   - Growth pattern – expansive or infiltrative.
   - Lympho-vascular invasion.
   - Presence of cysts, necroses or hemorrhages.
   - Status of the resection edges.
   - Metastases in lymph nodes and other organs, most often in the liver.
4. Immunohistochemical testing (at a consultative laboratory)
   - test for CD 117 (compulsory), CD34. If CD117 reaction is negative – apply PDGFR, DOG-1 and/or PKC teta.
   - markers for myogenic (desmin, SMA) and neurogenic (S-100protein) tumors
   - markers for differential diagnosis with fibroblast , lipoblast, melanotic and others tumors.
5. Defining the prognostic and predictive factors and the risk for recurrence in completely removed tumors according to the presented table
   - site, size, number of mitoses (proliferative index).
6. Diagnosis, CD117 expression, resection edges, prognostic category.
7. Recommendation for establish genetic mutations.

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Allergic Manifestations In Professionally Toner Exposed Persons

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РЕЗЮМЕ

Научно-техническият прогрес и революцията в информационните технологии родиха нова патология, обусловена от професионалната експозиция на суровини и материали използвани в производството и функционирането на копирните устройства.

Независимо от опита на редица страни, вкл. САЩ, Русия и някои страни от ЕС да регламентират по законодателен път стандарти, норми и правила за безопасност на работа, рискът от увреждане е налице.

Този риск нараства, като се има предвид обстоятелството, че редица субстанции са с все още слабо проучено въздействие върху здравето на човека. От друга страна не са напълно изяснени и взаимодействията между материали, апаратура и неблагоприятно действащите фактори от работната среда.

Този проблем важи с пълна сила за копирните устройства и материалите, използвани при работа с тях.

Ключови думи: тонер, професионална експозиция, алергия

ABSTRACT

Scientific and technological progress and revolution in information technologies have given way to a new pathology, caused by the professional exposure to materials and supplies used in manufacturing and functioning of copying machines.

Despite the attempts of a number of countries, incl. USA, Russia and some member countries of the EU, to produce a legal frame for standards, norms and safety rules during the working process, there is always a certain risk of damage. This risk is even higher having in mind the fact that a number of substances are still with poorly studied influence on human health. Interactions between materials, machines and adverse external factors from the working environment are yet to be studied as well.

This problem is very common with copying machines and their supplies.

Key words: toner, professional exposure, allergy

INTRODUCTION

Copying machines have been an integral part of our daily lives for a long time. They have entered intensively many professions in the field of intellectual work. Managers, technical staff, accountancy and archives, secretaries and recording secretaries – these are only part of the professions using copying technologies. The operators on copying machines, though, are particularly and most often in professional contact with copying machines and the materials used for their functioning. They are professionally exposed both to the factors, typical for their job, i.e. the toner from the ink cartridges for the copiers, and to a number of factors originating from the micro-

climate of the working environment – temperature and humidity in working spaces, dust, noise exposure, chemical contaminants from internal and external sources, biological factors, etc.

The toner is powder substance used in laser printers and copying machines in order to print a certain text or image on paper /1/.

From a chemical point of view it is a compound of carbon and different polymers which companies producing copying machines add to the carbon in order to improve its qualities. Such polymers could be for instance styrene-acrylate copolymer, polyester resin, styrol-butadiene, etc. In order to achieve higher resolution of the image, the size of the powder particles is significantly reduced to 8–10 micrometres for 600 pixels per inch resolution. Inhaling this fine powder by persons with respiratory diseases like asthma of bronchitis may lead to exacerbation of their existing health conditions /1, 2/. Latest studies show that submicroscopic particles that some laser printers exude can also cause respiratory diseases /3/. Besides the already known health risks, some authors have established that the microscopical particles in the toner have carcinogenic effects, like asbestos /4/.

Studies have shown that professionally exposed to laser printers office workers inhale high levels of nanoparticles that are refused in the air. This represents a health risk.

Some rare forms of health damage are established in professionally exposed to photocopiers persons, like the antiphospholipid syndrome /8/.

From a scientific point of view, there is a scientific interest for the mechanisms that lead to manifestation of the particular clinical symptoms in a patient.

It is also important to clarify the role of the etiologic factor for a certain individual – to what extent the leading role is that of the professional exposure to substances with certain physical and chemical properties, as in the case with toner, or is the dominating role that of the shifts in the working conditions and microclimate of the working environment.

The clinical cases, presented here within, supplement the manifold publications /1,2,3,4 ,5,6,7,8,9,10,11,12,13,14,15/ on this problem, enlarging the scientific knowledge on etiology, clinical manifestation and diagnostics of such damages.

CASE PRESENTATION 1

Female, aged 42 yrs /№ 10714 / 74/, hospitalized in the Department of Allergology at the Clinic for Professional Diseases on 23.02.2009.

Diagnosis at acception: Asthma, unspecified.

MATERIAL AND METHODS:

1. Occupational history:

First manifestation of the disease: 2 yrs ago when she suffers asthma attack due to massive exposure to pollen in month of May, clinical symptoms are pain (constrictions) in the chest, shortness of breath, dry irritating cough, lost of voice.

During her work with toner, with which the patient is in daily professional contact, she suffers cough, shortness of breath, lost of her voice.

There is explosive sneezing in contact with pine and lime. Later the symptoms are further exacerbated by inhaling typical aromas of perfumes, deodorants, household fresheners; in the last two months – during her work with photocopier and laser printer.

Total working experience – 18 yrs, of which 4 yrs of welding plates. In the last 10 yrs she has been working as a technical secretary.

Family history: No family history of immune and allergy pathologies.

Other accompanying risk factors: Active smoker since 4 yrs. Smokes 4–5 cigarettes a day.

Other respiratory diseases have not been established until present hospitalization.

2. Physical examination:

General condition is satisfying. Clear mind. Adequate. Afebrile. Pale skin and visible mucous membranes. Tongue and speech – no peculiarities. Slightly diffusely enlarged thyroid gland I – II degree, palpably sensitive. Periodically dry and irritable cough. Difficulties in expectoration. Peripheral

lymph nodes – not palpable. Respiratory system: symmetrical chest halves. Sonoran perkutoral tone. Slightly weakened in the bilateral lung bases vesicular breathing, without wheezing.

Cardiovascular system: rhythmical heartbeat, normofrequent. Heart rate 72 beats per minute. Clear heart tones. RR: 100/70 mmHg.

Succ. renalis bilateral. /–/ negative.

Abdomen – soft, not painful in palpation. Liver – not enlarged. Spleen – not palpable.

3. Diagnostic procedures:

– Blood tests:

Haematological: RBC – 4.34 T/ L, WBC – 3.82 G/ L, HGB – 102 g/l, HCT – 0.330, PLT – 263 G/L, MCV – 76.0, ESR – 10 mm.

Diff. morph.count: Neut. – 49.5%, Lymph. – 38.4%, Eos. – 1.6%, Mono. – 9.2%, Baso. – 1.3%.

Biochemical: Tot. prot. – 79 g/l, gluc. – 4.9 mmol/l, urea – 3.8 mmol/l, creat. – 72 mkmol/l, t. bill. – 5.8 mkmol/l, AST – 22 U/l, ALT – 12 U/l.

Immunological: Tot.IgE – 5.40 IU/mL / в норма /. C3 – 1.13, C4–0.38 g/l /within normal range/.

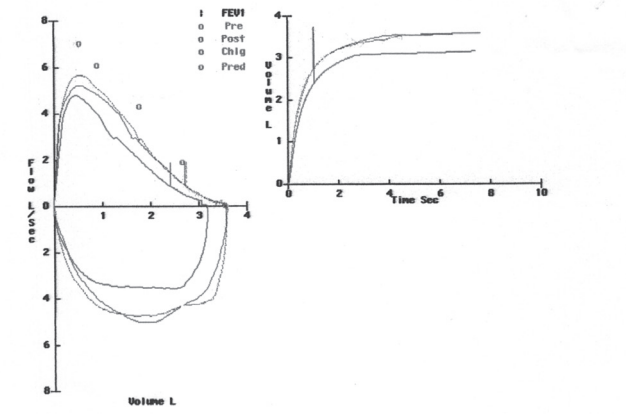
- Frontal pulmography: Pulmonary emphysema. Peribronchial changes.
- Spirometry conclusion: Lung ventilation at rest – normal.
- Bronchoprovocation test with Methacholine: Results from Bronchoprovocation test are 11% drop of FEV1 with dosage of Methacholine of 4 mg/ml. Due to strong cough, lost of breath and dry voice further testing was terminated.
- Testing for skin allergies with standard set of allergens proved sensitization to city, summer, grass, tree and late summer pollens.
- Patch test with standard set of allergens is negative /–/.

Medical University of Plovdiv Pathophysiology Dept. CPET Laborator
Challenge Spirometry Date:February 26, 2009 12:59
For Patient: Stefanova, Galina Ivanova

Dr: S. Mandadjieva, MD BMI - 21.1 Ht: 170.0 cm Age: 42 yr
ID: BPr_371 BSA - 1.71 Wt: 61.0 kg Sex: F

SPIROMETRY

		PRE-BRONCH			POST-BRONCH		CHALLENGE	
		Actual	Pred.	%Pred.	Actual	%Chg	Actual	%Chg
FVC	(L)	3.60	3.55	101	3.57	-1	3.17	-12
FEV1	(L)	2.72	3.06	89	2.74	1	2.41	-11
FEV1/FVC	(%)	76	81		77	1	76	1
FEF 25%	(L/sec)	4.84	6.02	80	5.13	6	4.23	-13
FEF 50%	(L/sec)	2.70	4.28	63	2.83	5	2.39	-11
FEF 75%	(L/sec)	0.93	1.84	51	0.94	1	0.88	-5
FEF Max.	(L/sec)	5.19	6.98	74	5.63	8	4.77	-8
FEF 25-75%	(L/sec)	2.25	3.62	62	2.33	4	2.00	-11
FIVC	(L)	3.59			3.61	1	3.20	-11
FIF 50%	(L/sec)	5.03	3.77	133	4.75	-6	3.51	-30
FEF 50%/FIF 50%		0.54	1.14		0.60	11	0.68	26
SVC	(L)	3.33	3.55	94				
IC	(L)	2.62	2.65	99				
ERV	(L)	0.71	0.90	79				



CASE PRESENTATION 2

Male, 21 yrs. / № 53669/287 / , hospitalized in UMBAL „St. George“, Plovdiv, Department for Professional diseases and Allergology on 29.09.2011

Diagnosis at acception: Asthma, unspecified.

MATERIAL AND METODS:

1.Occupational history:

First complaints appear 2 months before, when he had an attack of expirational shortness of breath, wheezing, constrictions in the chest. Periodically a cough appeared, mostly irritable and non-productive. In some cases there is yellowish secretion.

Since 4 months he has been working as an operator on a copier machine. The patient is professionally exposed to toner. He reports episodes of shortness of breath and chest constrictions during working process.

Accompanying rhinitis symptoms which first appear in childhood are continuing. They manifest in itchy nose, sneezing, excessive watery secretion, periods with „stuffy nose“. Post nasal drip. Symptoms are during all seasons, but particularly noticeable during spring mainly in the period of active pollination of poplars. He reports episodes of exacerbation of nasal problems, irritation behind the breastbone and dry cough at a contact with toner. Complaints

occur also in indirect exposure to vapors of chlorinated chemicals from a neighboring dry cleaner's office.

No reports for medical intolerance.

Family history: No family history of immune and allergy pathologies.

Other risk factors: For three years he has been smoking up to 5 cigarettes a day. Since 4 months he is a non-smoker.

2.Physical examination:

In good general condition. Clear mind. Adequate. Afebrile. White skin. Pale pink visible mucous membranes. Tongue and speech – no peculiarities. Peripheral lymph nodes – not palpable.

Respiratory system: Chest is with correct shape. Symmetrical chest halves. Sonoran perkutoral tone. Slightly weakened in the bilateral lung bases vesicular breathing. No sound of wheezing.

Cardiovascular system: rhythmical heartbeat, normofrequent. Heart rate 80 beats per minute. Clear heart tones. RR: 125/85 mmHg.

Succ. renalis bilateral. /–/ negative.

Abdomen – soft, not painful in palpation. Liver – not enlarged. Spleen – not palpable. Musculo-skeletal system – properly developed.

3.Diagnostic procedures:

Blood test:

Hematological: RBC – 5.75 T/l., HGB – 164 g/l, WBC – 8.10 G/l., HCT – 0. 492 , MCV – 85.6, MCH – 28.6, PLT – 304 G/l. , ESR – 2 mm.

Diff.morph.count: Neut. – 61.3 % , Mono. – 4.9 % , Lymph. – 27.1 %, Eos. – 3.1 %, Baso – 0.7%

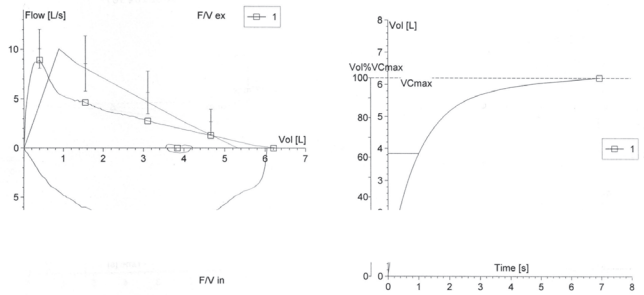
Biochemical: gluco. – 4.6 mmol/l.,t.prot. – 77g/l, alb. – 45 g/l, urea – 4.9 mmol/l, crea – 66 mkmol/l, GGT – 27 U/L, ALP – 168 U/L, CK – 129 U/L, AST – 18 U/L, ALT – 21 U/L.

Immunological: Tot.IgE – 122.15 IU/mL / within normal range /.

MEDICAL UNIVERSITY OF PLOVDIV
DEPARTMENT OF PATHOPHYSIOLOGY
PULMONARY FUNCTION LABORATORY

Flow-Volume Curves and Values

Last Name:	Nyagolov	Identification:	22529
First Name:	Nikolaj Denchev	Ward:	Prof&Toxicology
Sex:	male	Age:	21 Years
Smoker:	Yes	Height:	179,0 cm
Diagnosis:	Asthma Bronch	Weight:	87,0 kg
Phone:	0884033185	Free:	9002184367

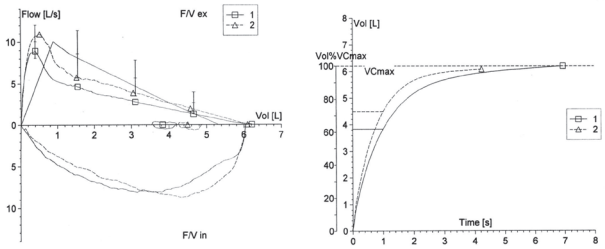


		PredLL	Act1	%(A1/P)
VC MAX	[L]	4.65	6.21	111.5
IC	[L]	3.97	4.47	112.7
ERV	[L]	1.71	1.74	101.4
FVC	[L]	4.32	6.21	116.7
FEV 1	[L]	3.65	3.84	85.6
FEV 1 % FVC	[%]		61.79	
PEF	[L/s]	8.08	8.92	88.6
FEF 25	[L/s]	5.77	4.62	53.9
FEF 50	[L/s]	3.49	2.76	48.7
FEF 75	[L/s]	1.40	1.28	47.6
MMEF 75/25	[L/s]	3.39	2.44	47.9
FET	[s]		6.94	
FEV PEF	[L]		0.40	
FET PEF	[s]		0.04	
TC 25/50	[s]		1.05	
Mean transit time	[s]	0.45	1.15	199.9
Exspir. F/V area	[L*L/s]	31.37	19.20	61.2
PIF	[L/s]		8.14	
FIF 50	[L/s]		8.01	
FIV1	[L]		5.89	
FEF50 % FIF50	[%]		34.43	
Date			29.09	
Time			11:09	

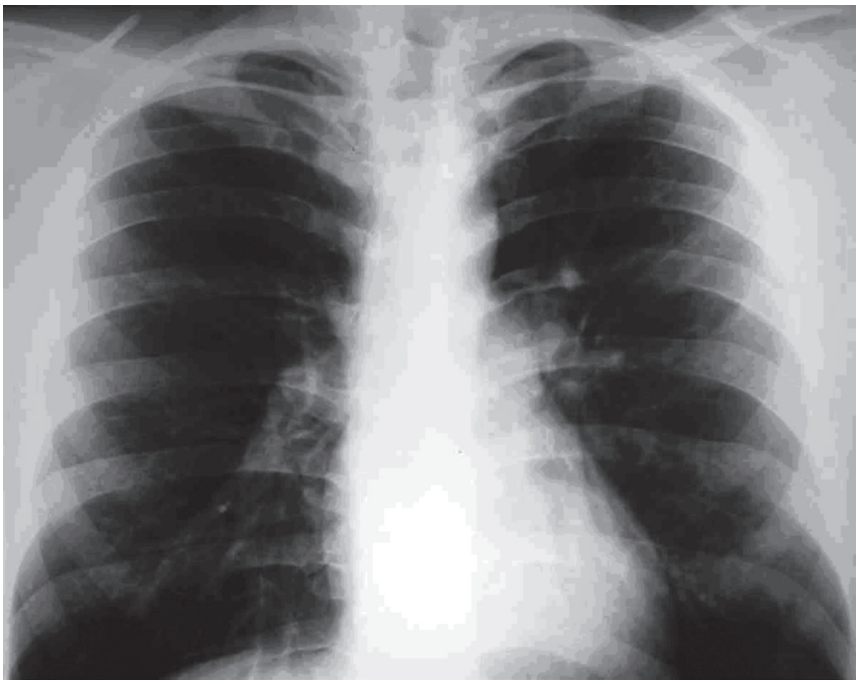
MEDICAL UNIVERSITY OF PLOVDIV
DEPARTMENT OF PATHOPHYSIOLOGY
PULMONARY FUNCTION LABORATORY

Flow-Volume Curves and Values - Post BDT

Last Name:	Nyagolov	Identification:	22529
First Name:	Nikolaj Denchev	Ward:	Prof&Toxicology
Sex:	male	Age:	21 Years
Smoker:	Yes	Height:	179,0 cm
Diagnosis:	Asthma Bronch	Weight:	87,0 kg
Phone:	0884033185	Free:	9002184367



		Act1	%(A1/P)	Act2	%(A2/P)	Delta%(D/P)
VC MAX	[L]	6.21	111.5	6.09	109.4	-0.12 -2.08
IC	[L]	4.47	112.7	4.92	124.0	0.45 11.36
ERV	[L]	1.74	101.4	1.17	68.3	-0.57 -33.1
FVC	[L]	6.21	116.7	6.09	114.5	-0.12 -2.18
FEV 1	[L]	3.84	85.6	4.49	100.2	0.66 14.64
FEV 1 % FVC	[%]	61.79		73.74		11.94
PEF	[L/s]	8.92	88.6	10.93	108.6	2.01 20.01
FEF 25	[L/s]	4.62	53.9	5.73	66.8	1.11 12.97
FEF 50	[L/s]	2.76	48.7	3.84	67.9	1.08 19.14
FEF 75	[L/s]	1.28	47.6	1.94	72.4	0.67 24.83
FET	[s]	6.94		4.24		-2.70
FEV PEF	[L]	0.40		0.52		0.12
FET PEF	[s]	0.04		0.05		0.00
TC 25/50	[s]	1.05		0.80		-0.25
Mean transit time	[s]	1.15	199.9	0.73	127.7	-0.42 -72.2
Exspir. F/V area	[L*L/s]	19.20	61.2	25.70	81.9	6.50 20.73
PIF	[L/s]	8.14		8.73		0.59
FIF 50	[L/s]	8.01		7.39		-0.62
FIV1	[L]	5.89		5.79		-0.10
FEF50 % FIF50	[%]	34.43		51.99		17.56
Date		29.09		29.09		
Time		11:09		11:32		



Patch – test with standard set of professional allergens

№	Allergen	Results 48th hour
1	Potassium dichromate	–
2	4 – phenylendiamine base /PPD/	–
3	Thiuram mix	–
4	Neomycin sulfate	+
5	Cobalt /II/ chloride hexahydrate	+
6	Benzocaine	+
7	Nickelsulfate hexahdrate	+
8	Clioquinol	+
9	Colophony	+
10	Paraben mix	–
11	N-isopropyl-N-phenyl-4-phenilendiamine / IPPD/	–
12	Lanolin Alcohol	–
13	Mercapto mix	+
14	Epoxy resin	+
15	Balsam Peru	–
16	4-tert-Butylphenolformaldehyde resin	–
17	2-Mercaptobenzothiazole /MBT/	+
18	Formaldehyde	+
19	Fragrance mix I	+
20	Sesquiterpene lactone mix	+
21	Qua ternium 15	+
22	2-methoxy-6-n-penthyl-4-benzoquinone / Primin/	–
23	5-chloro-2-methyl-4-benzoquinone /Kathon CG/	+
24	Budesonide	+
25	Tixocortol-21-pivalate	–
26	Methyldibromoglutaronitrile	–
27	Fragrance mix II	+
28	Lyral /alpha-hexyl cinnamal /	+

Patch test with materials withi which the patient is in direct professional or indirect contact

Material	Results 48th hour
Powder substance of toner /direct contact/	–
Perchlorate /indirect contact/	+

Skin allergy samples with standard set of allergens

Allergen	Type of sample	Results 20 min.
A1 house dust	intradermal	25/20 Extremely positive
A2 down, feathers	intradermal	/–/ Negative
Д7 Candidin	intradermal	20/15 Very positive
Б3 spring pollen	Prick test	20/20 Very positive
Б4 summer pollen	Prick test	25/25 Extremely positive
Б5 late summer pollen	Prick test	25/25 Extremely positive
Dermatophagoides	Prick test	15/15 Extremely positive
City mold allergen 1	intradermal	/–/ Negative
City mold allergen 2	intradermal	/–/ Negative
Pet allergens: – Dog hair – Cat hair	intradermal	/–/ Negative

TREATMENT REGIMEN:

Therapeutic scheme in both patients includes application of fast-acting beta-2-mimetic (agonist) – Salbutamol inhaler /BUTO-ASMA/ 0.1 mg/dose – if necessary. Systemic corticosteroid /Dexamethasone/ was applied in dosage, relevant to the clinical condition, physical findings and pulmonary function indicators. Therapeutic course with H1 blockers has been assigned after results from Skin – allergens testing.

OUTCOME OF THE HOSPITALIZATION:

Both patients are discharged in good general condition with no symptoms.

DISCUSSION:

1. The symptoms registered in the presented cases can be organised in two groups:
   - from upper respiratory tract, clinically manifested mostly as rhinitis and rhinopharyngitis: excessive watery rhinorrhoea, itchy nose, sneezing, nasal congestion, irritable throat, dysphonia;
   - from lower respiratory tract, clinically manifested with some of the typical asthma stigmas: shortness of breath, chest constrictions, cough, episodes of weezing.

2. Allergic origin of diagnosed problems is confirmed by the carried out clinical examinations, tests and samples, and mostly by the results from the skin-allergy tests and provocative tests, which indicate the atopy in the patients examined. The professional exposure to toner most probably triggers the manifested symptoms against the increased reactivity of the respiratory tract.

3. The adverse influence of toner on lungs is confirmed by some experimental studies which have proved cases of pulmonary fibrosis /14/.

4. It is quite possible that the toner, due to its physical and chemical properties and its chemical compounds, irritates upper respiratory tract.

5. In a number of publications copying machines are considered to be a factor, causing air pollution in buildings and working areas /9,10/. Some components of working environment influence air quality in closed working areas, such as inadequate ventilation, chemical contaminants from inner and outer sources, biological contaminants, etc. They can additionally influence reactivity of respiratory tract in different ways: neuro-reflectoral, toxic or any other yet unknown.

6. Despite the fact that in the presented cases there are no available results from laboratory tests of work environment factors, the influence of the so-called „Sick building syndrome" cannot be excluded as a possible cause. In this syndrome the adverse effects on the health of workers are due to some nonspecific changes caused by the parameters of the production microclimate.

CONCLUSION:

1. The cases presented here within prove that toner which is used in many types of copying machines can cause a number of respiratory symptoms in professionally exposed persons.
2. Taking targeted history of the patient during which the nature of the profession and the risk factors of the work environment are specified is of prime importance for diagnostics in problems of similar origin.
3. The presented cases enlarge the scientific knowledge and would be useful both for general practitioners, and for the physicians working in Occupational health services.
4. Timely and adequate diagnostic clarification in patients with nonspecific complaints in upper and lower respiratory tract who are professionally exposed to toner in copying machines, calls for an expertise by the relevant specialists – profpathologists and allergists.

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The size of each paper should not exceed 10 pages (up to 5 000 words) for original research articles, 12 pages for reviews (7 500 words), 3 pages for case reports, 2 pages for short communications, 4 pages for discussions or correspondence on scientific events on medical books or chronicles. The references or illustrations are included in this size (two 9x13 cm figures, photographs, tables or diagrams are considered as one standard page).

The abstracts are not included in the size of the paper and should be submitted on a separate page with 3 to 5 key words at the end of the abstract. They should reflect the most essential topics of the article, including the objectives and hypothesis of the research work, the procedures, the main findings and the principal conclusions. The abstracts should not

Списание „Българска медицина", издание на Българската Академия на Науките и Изкуствата, Отделение за наука, Научен център по медицина и здравеопазване, излиза в четири книжки годишно. „Българска медицина" е достъпна онлайн на сайта на БАНИ, раздел издания.

В него се отпечатват оригинални научни статии, казуистични съобщения, обзори, рецензии и съобщения за проведени или предстоящи научни конгреси, симпозиуми и други материали в областа на клиничната и фундаменталната медицина. Списанието излиза на английски език с подробни резюмета на български и английски. Изключения се правят за обзорни статии по особено значими теми. Заглавията, авторските колективи, а също надписите и означенията на илюстрациите и в таблиците се отпечатват и на двата езика.

Материалите трябва да се предоставят в два еднакви екземпляра, напечатани на пишеща машина или на компютър, на хартия формат А4 (21 х 30 см), 60 знака на 30 реда при двоен интервал между редовете (стандартна машинописна страница). Освен това могат да бъдат изпратени като прикачени файлове по електронната поща на адресите, посочени по-долу.

Обемът на представените работи не трябва да превишава 10 стандартни страници за оригиналните статии (или 5000 думи според стандарта на англосаксонските издания) 12 страници (7 500 думи) за обзорните статии, 3–4 страници за казуистичните съобщения, 4 страници за информации относно научни прояви в България и в чужбина, както и за научни дискусии, 2 страници за рецензии на книги (монографии и учебници). В посочения обем се включват книгописът и всички илюстрации и табли-

exceed one standard typewritten page of 200 words.

The basic structure of the manuscripts should meet the following requirements:

Title page

The title of the article, forename, middle initials (if any) and family name of each author; institutional affiliation; name of department(s) and institutions to which the work should be attributed, address and fax number of the corresponding author.

Text of the article

Titles and subtitles should be standardized.

The original research reports should have the following structure: introduction (states the aim, summarizer the rationale for the study), subjects and materials, methods (procedure and apparatus in sufficient detail, statistical methods), results, discussion, conclusions (should be linked with the aims of the study, but unqualified statements not completely supported by research data should be avoided). These requirements are not valid for the other types of manuscripts. Only officially recognized abbreviations should be used, all others should be explained in the text. Units should be used according to the International System of Units (S. I. units). Numbers to bibliographical references should be used according to their enumeration in the reference list.

Illustrations

Photographs should be presented both in the text body to indicate their location and in separate files as saved in jpeg, tif or bitmap formats.

The figures, diagrams, schemes, photos should be submitted in a separate file with: consecutive number (in Arabic figures); titles of the article and name of the first author. The explanatory text accompanying the figures should be presented along with the respective number of the figure in the main text body with space left for insertion of the figure.

ци. В същия не се включват резюметата на български и английски, чийто обем трябва да бъде около 200 думи за всяко (25–30 машинописни реда).

Резюметата се представят на отделни страници.Те трябва да отразяват конкретно работната хипотеза и целта на разработката, използваните методи, най-важните резултати и заключения. Ключовите думи (до 5), съобразени с „Medline“, трябва да се посочат в края на всяко резюме.

Структурата на статиите трябва да отговаря на следните изисквания:

Титулна страница

а) заглавие, имена на авторите (собствено име и фамилия), название на научната организация или лечебното заведение, в което те работят. При повече от едно заведение имената на същите и на съответните автори се маркират с цифри или звездички;

б) същите данни на английски език се изписват под българския текст.

Забележка: при статии от чужди автори българският текст следва английския. Точният превод от английски на български се осигурява от редакцията. Това се отнася и за останалите текстове, включително резюметата на български.

Основен текст на статията

Заглавията и подзаглавията следва да бъдат уеднаквени и различими.

Оригиналните статии задължително трябва да имат следната структура: увод, материал и методи, собствени резултати, обсъждане, заключение или извод.

Методиките следва да бъдат подробно описани (включително видът и фирмата производител на използваните реактиви иапаратура). Същото се отнася и за статистическите методи.

Тези изисквания не важат за обзорите и другите видове публикации. В текста се допускат само официално приетите международни съкращения; при използване на дру-

References

The references should be presented on a separate page at the end of the manuscript. It is recommended that the number of references should not

Exceed 20 titles for the original articles and 40 titles for the reviews; 70 % of them should be published in the last 5 years. References should be listed in alphabetical order, English first, followed by the Bulgarian ones in the respective alphabetic order. The number of the reference should be followed by the family name of the first author and then his/her initials, names of the second and other authors should start with the initials followed by the family names. The full title of the cited article should be written, followed by the name of the journal where it has been published (or its generally accepted abbreviation), volume, year, issue, first and last page. Chapters of books should be cited in the same way, the full name off the chapter first, followed by"In:" full title of the book, editors, publisher, town, year, first and final page number of the cited chapter.

Examples:

Reference to a journal article:

1. McLachan, S. , M. F. Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Reference to a book chapter:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Submission of manuscripts

The original and one copy of the complete manuscript are submitted together with a covering letter granting the consent of all authors for the publication of the article as well as a statement that it has not been published previously elsewhere and signed by the first author. The procedure should be complemented via electronic submission. Manuscripts of

ги съкращения те трябва да бъдат изрично посочени в текста. За мерните единици е задължителна международната система SI. Цитатите вът-ре в текста е препоръчително да бъдат отбелязвани само с номерата им в книгописа.

Илюстрации и таблици

Снимките – освен в Word, за да се знае местоположението им, следва да бъдат предоставени и като отделни файлове във формат jpg, tif или bitmap.

Илюстрациите към текста (фигури, графики, диаграми, схеми и др. черно-бели копия с необходимия добър контраст и качество) се представят на отделни листове (без обяснителен текст), в оригинал и две копия за всяка от тях. Текстът към фигурите със съответната им номерация (на български и на английски език) се отбелязва вътре в основното текстуално тяло на статията под съответния номер на мястото, където трябва да се разположи при предпечатната подготовка.Таблиците се представят с готово написани обяснителни текстове на български и на английски, които са разположени над тях; номерацията им е отделна (също с арабски цифри).

Използвана литература:

Книгописът се представя на отделен лист. Броят на цитираните източници е препоръчително да не надхвърля 20 (за обзорите до 40), като 70 % от тях да бъдат от последните 5 години. Подреждането става по азбучен ред (първо на латиница, после на кирилица), като след поредния номер се отбелязва фамилното име на първия автор, след това инициалите му; всички останали автори се посочват с инициалите, последвани от фамилното име (в обратен ред) до третия автор, последвани от съкращшениетоет Al. Следва цялото заглавие на цитираната статия, след него названието на списанието (или общоприетото му съкращение), том, година, брой на книжката, началната и

articles accepted for publication will not be returned to the authors.

Peer-review process

Following the international standards in the field, the Editorial board has adopted double-blind peer-review policy assigned to independent referees. The authors are encouraged to submit the names of three potential referees for editorial consideration

Following acceptance for publication the authors are charged 5 euros per page for language editing and corrections.

Ethical regulations: reports with experiments on human subjects should specify whether the procedures were conducted in accordance with the ethical norms if the responsible committee on Human experimentation (local or regional) and/or with the Helsinki Declaration, as revised in 2000. Respective guidelines for animal experimentation should be considered.

Address for sending of manuscripts and other editorial correspondence

1431 Sofia, Zdrave str. 2,
University Hospital for Endicrinology
And the next electronic addresses:
Prof. Dr Philip Kumanov, Editor-in-chief:
phkumanov@lycos.com

With copy for the scientific secretary –
Assoc. Prof. Drozdstoj Stoyanov:
stojanovpisevski@gmail.com

крайната страница. Глави (раздели) от книги се изписват по аналогичен начин, като след автора и заглавието на главата (раздела) се отбелязват пълното заглавие на книгата, имената на редакторите (в скоби), издателството, градът и годината на издаване, началната и крайната страница.

Примери:

Статия от списание:

1. McLachlan, S., M. F.Prumel, B. Rapoport. Cell Mediated or Humoral Immunity in Graves' Ophthalmopathy? J. Clin. Endocrinol. Metab., 78, 1994, 5, 1070–1074.

Глава (раздел) от книга:

2. Delange, F. Endemic Cretenism. In: The Thyroid (Eds. L. Braveman and R. Utiger). Lippincott Co, Philadelphia, 1991, 942–955.

Адрес за кореспонденция с авторите

Той се дава в края на всяка статия и съдържа всички необходими данни (вкл. електронна поща) на български език за един от авторите, който отговаря за кореспонденцията.

Всички ръкописи трябва да се изпращат с придружително писмо, подписани от авторите, с което потвърждават съгласието си за отпечатване в сп. „Българска медицина". В писмото трябва да бъде отбелязано, че материалът не е бил отпечатван в други научни списания у нас и в чужбина. Ръкописи не се връщат.

Процедура по рецензиране:

С оглед спазване на международните стандарти, редакционната колегия е приела процедура по 'двойно сляпа' рецензия от независимио референти. На авторите се предоставя възможноста да предложат на вниманието на редакционния екип три имена на специалисти в тяхната област като потенциални рецензенти.

След положителна рецензия и одобрение на редколегията, авторите на статията дължат заплащане в размер на 10 лв. за вся-

ка стандартна машинописна страница, с оглед на покриване разноските по английска езикова редакция на текста и коректури.

Етически съображения

Всички трудове, които отразяват експерименти с хора следва да бъдат съобразени с етическите норми и регулации, въведени от съответния местна или регионална научна комисия и/или с Декларацията от Хелзинки, ревизия от 2000г. Експериментите с животни следва да бъдат също така съобразени със съответните норми и правила.

Всички материали за списанието се изпращат на посочения адрес:

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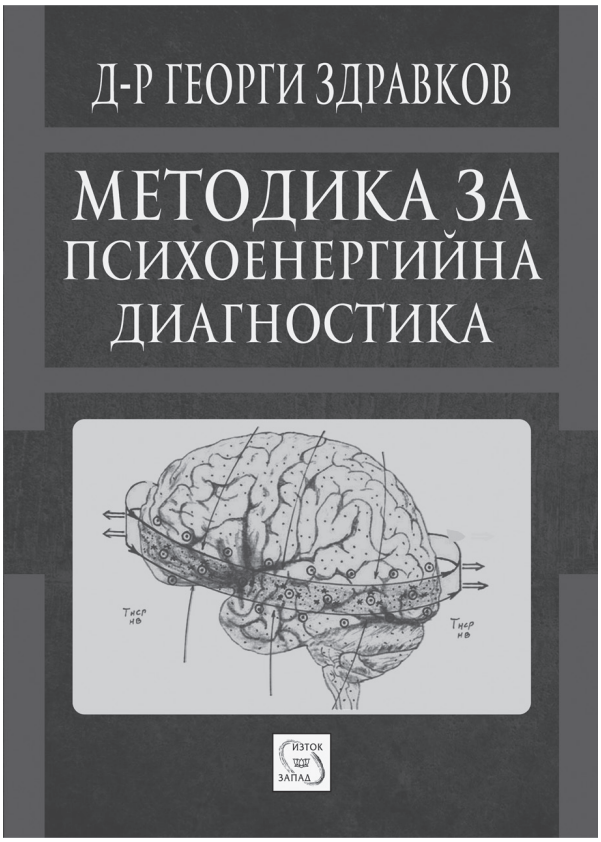
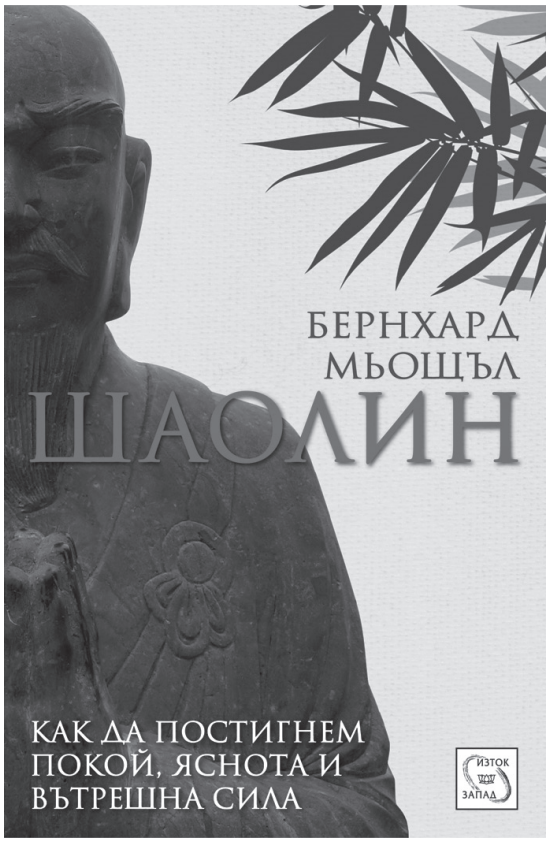
1431 София, ул. Здраве 2, УСБАЛЕ
или на следния електронен адрес:
phkumanov@lycos.com

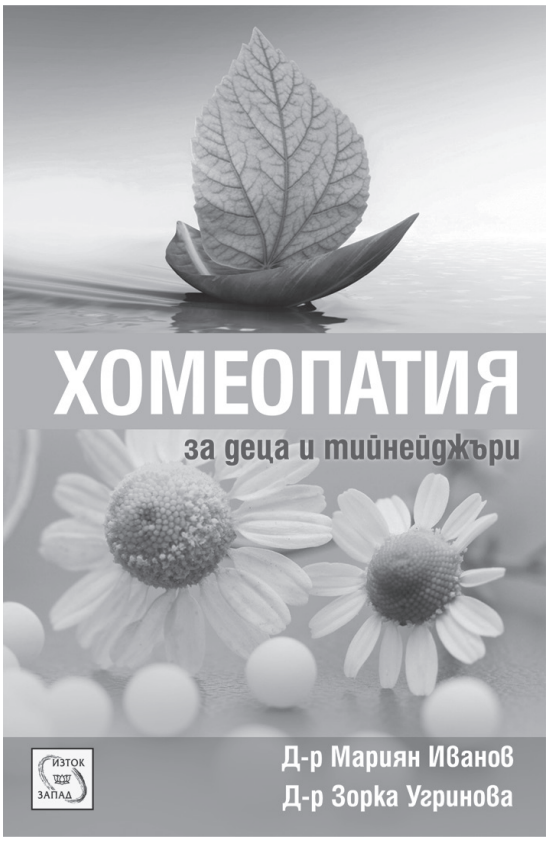
С копие до научния секретар –
Доц. Д-р Дроздстой Стоянов:
stojanovpisevski@gmail.com

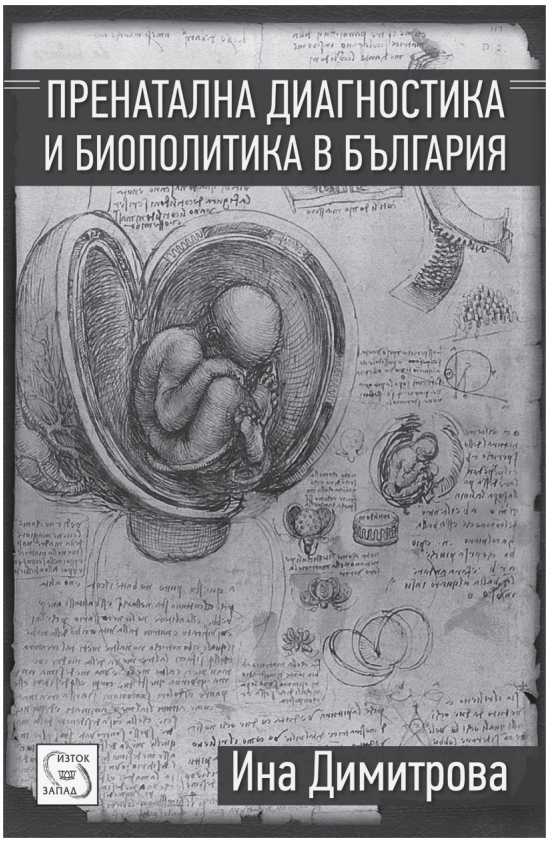

ЛОРЪНС КОЕН
ДЕЦАТА, РОДИТЕЛИТЕ, ИГРАТА
ТАЙНИТЕ НА ИГРОВИЯ ПОДХОД
ИЗТОК ЗАПАД


Д-Р ГЕОРГИ ЗДРАВКОВ
МЕТОДИКА ЗА ПСИХОЕНЕРГИЙНА ДИАГНОСТИКА
ИЗТОК ЗАПАД


БЕРНХАРД МЬОЩЪЛ
ШАОЛИН
КАК ДА ПОСТИГНЕМ ПОКОЙ, ЯСНОТА И ВЪТРЕШНА СИЛА
ИЗТОК ЗАПАД

In omnia paratus





„Патологията е основа на всички медицински познания“

проф.д-р Карл Рокитански

Излезе III-то издание на „Клинична патология“ с редактори акад. Григор Велев и акад.Маргарита Каменова, предназначен за студенти по медицина и стоматология, лекари и специалисти по обща и клинична патология. Клиничната патология е вторият важен раздел, след общата част, от основната медицинска дисциплина „патология“, който има за предмет изучаване на морфологичния субстрат на клинично обособените нозологични единици- болестите. Съвременната патология отдавна излезе от рамките на макроскопската диагностика , свеждаща се до описание и диагностика на анатомичните промени, настъпили в резултат на патологичните процеси или болестта. Днес в патологията навлязоха и намират приложение редица нови модерни методи за изследване и диагностика , които позволяват проучването на морфологичния субстрат да се извършва не само на клетъчно и субклетъчно, но и на молекулярно ниво. Освен това обект на диагностика са клинично обособени нозологични единици- болестите. С клиничната патология се определят двете главни характеристики на заболяванията – вида и локализацията на болестн ия процес. Чрез морфологичното изследване на резекционен материал и използване на разнообразни инвазивни диагностични методи- тънкоиглена аспирационна биопсия, пункционна биопсия, ендоскопски методи и други се извършва диагноза на всички органи и системи в човешкото тяло. Патологията е съществена и неделима част от хирургичната дейност и особено в онкологията, при която правилния избор на лечение и прогнозната оценка се базират на данните от морфологичното изследване.

Предлаганият учебник по **„КЛИНИЧНА ПАТОЛОГИЯ“** е написан от изтъкнати преподаватели и специалисти в различни области на диагностичната патология. Това допринесе да се направи системно и компетентно изложение на материята. В учебника са представени освен класическите и утвърдени от практиката знания и нова съвременна информация.

В настоящето, III издание , са направени съществени допълнения и преработки, продиктувани от необходимостта от актуализиране на информацията. Основно са преработени главите за клинична патология на сърцето и на нервната система с включване на нови нозологични единици от патологията на периферната и симпатикова нервна система. Допълнени са съвременни данни за белодробните карциноми, туморите на плеврата, туморите на носа и параназалните синуси, уротелните и бъбречни тумори, карцинома на простатната жлеза и са направени други по-малки допълнения в онкопатологията. Въведена е информация за някои нови и/или особено актуални за клиниката заболявания,например за гастроинтестиналните стромални тумори /ГИСТ/, които отскоро бяха обособени в самостоятелна туморна група, алергичния алвеолит, както и новата концепция за невроендокринните тумори. Главата „инфекциозни болести“ е попълнена с данни за цитомегалията , некротичния фасциит и актиномикозата, а полиетиологичното заболяване сепсис е разгледано в съвременните аспекти на неговата терминология, класификация и патогенеза. Преработена и съкратена е главата за туберкулозата с оглед по-ясното и достъпно изложение на материала. Избегнато е също дублирането на някои заболявания. С преработеното и допълнено с актуална информация трето издание студентите медици, стоматолози и лекарите от практиката получават модерно ръководство за усвояване на знанията по клинична патология, фундамент на медицинската наука и практика.