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CURRICULUM VITAE

PIETRO BRACCO

Graduated in Medicine in 1967, specialized in Prosthetic Dentistry in 1969 at the University of Turin and in Orthodontics, in 1979, at the University of Milano.
He was the Director of the Dental School from 1992 through 1997, actually he is the Chairman of the Chair of Orthodontics and Gnathologymasticatory function and the Director of the Orthodontic School, of the II level Master in Orthodontics and of the PhD XXI cycle at the University of Turin.
He is the Chief of the Hospital Orthodontic Department.
He is the vice-president of the Orthodontists Union, he is an Ordinary member of the Italian Orthodontics Society, a Member of the International College of Dentists, a Member of the Turin Medicine Academy.

- Specialist in Dentistry and Dental Implants at the University of
- Turin; Specialist in Orthodontics University of Milan; Chair of Orthodontics and
- Gnathology Faculty of Medicine, Universityof Turin; CLOPD President of the University of Turin 1992 to 1997;
- Director of the School of Specialization in Orthodontics; Director of Master's Level Orthodontics – Masticatory Function, University of Turin; Coordinator of the PhD "Pathophysiology of mastication and dental materials of the masticatory-XXI-XXIII
- Cycle; International Research Framework Agreement with the University of Rochester
- New York USA; Director of the Department of Dentistry SC D.U. Orthodontics S.S.N. - Piedmont Hospital San Giovanni Battista di Torino; National Vice President of S.U.S.O. ; Full Member of S.I.D.O. (Italian Society of Orthodontics); Secretary of editing the journal Minerva
- Orthognathic "from 1983; Member of the International College of Dentists since 1982; Member of the Academy of Medicine of Turin; Master of International College of Cranio-Mandibular
- Orthopedics (I.C.C.M.O.); Holder of Diploma of Merit with a gold medal I; Class conferred by the Italian Red Cross in 1982; Promoter and owner of various and numerous studies for discussion specific topics in various working groups, with different skills, consisting of numerous students and former students of the School of Specialization in Orthodontics University Turin; Author and coauthor of over 300 scientific papers in national journals and
- international.

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CURRICULUM VITAE

DANIEL ROLLET

- 1978: Degree in Dental Surgery (Strasbourg);
- 1985: Specialist qualified Orthodontic (Graduated CECSMO - Strasbourg);
- Installed PONTARLIER since July 1982.

CURRENT TITLES

- President of the Society of BioProgress Ricketts 1995-2001 and since November 2007, and also a member.
- Holder of the Certificate of Excellence in Orthodontics: member of the Jury.
- Member of the Organizing Committee of Olympic Games (Days of Orthodontics).
- Expert to the Court of Appeal of Besançon on Social Security and judicial.
- Elected member of the Departmental Council (Vice President) and the Regional College of Dental Surgeons of Doubs.
- Member of the National Bureau of the Union of Specialists in Orthodontic.
- Instructor in the CERTOB Study Group with Dr. Carla Gugino and Michael Delamair.
- Lecturer at the Dental Faculty of Strasbourg.
- Member of AGORA (research group on élastopositionnement)
- Member of the French firm ODF
- Member of the Organizing Committee of the W.F.O. 2005
- Member of the National Bureau of F.F.O. (French Federation of Orthodontics).

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METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS ISOLATED FROM PATIENTS HOSPITALIZED IN THE INTENSIVE CARE UNIT (ICU)

F. HORHAT, LILIANA DRAGOMIRESCU, DELIA HORHAT, DELIA MUNTEANU, ELENA HOGEA, C. PILUT RODICA LIGHEZAN, V. DUMITRASCU, MONICA LICKER, ROXANA MOLDOVAN

Department of Microbiology and Virusology, University of Medicine and Pharmacy "Victor Babeş" Timişoara

Correspondence to:

Contact: Horhat Florin, E-mail: horhatflorin@yahoo.com, University of Medicine and Pharmacy "Victor Babeş" Timişoara, Department of Microbiology and Virusology, Tel +40722369675

ABSTRACT

Objective*. The objective of our study was to determine the prevalence of methicillin resistant S. aureus (MRSA) in ICU.*

Method*: We have evaluated 291 samples collected from 278 patients hospitalized in ICU Clinical Emergency County Hospital Timişoara, in the period of March-June 2009.*

Results*: From 271 positive samples (bronchoalveolar fluids, wound secretions, urines, blood, peritoneal fluids, catheter tips) we isolated 276 microbial strains with nosocomial potential, from wich 69 were Staphylococcus aureus strains.*

Conclusions*: In the Intensive Care Unit, Staphylococcus aureus was the second most frequent isolated pathogen, after Klebsiella pneumoniae.*

From 69 S. aureus strains, 30 were MRSA (43, 47%). In this study MRSA strains exhibit coresistance against kanamycin, gentamicin, tobramycin, ciprofloxacin, erythromycin and trimethoprim-sulphamethoxazole. We did not isolate any strain with linezolid, vancomycin, teicoplanin and fosfomycin or rifampicin resistance. These remain the drugs of choice for serious staphylococcal infections.

Key words: nosocomial infections, resistance phenotype, MRSA

INTRODUCTION

The global increase in antimicrobial resistance, including the emergence of multidrug resistance bacterial strains, has created a public health problem of potentially crisis proportions. Not long after penicillin was put into general use, Staphylococcus aureus strains were found which did not respond to treatment, and by 1950 penicillin resistant.

S. aureus was a common cause of infections in hospitals. A decade later, methicillin a semi-synthetic form of penicillin, was introduced; this was not affected by the β-lactamase enzymes that

inactivated Penicillin G, and was used to treat resistant forms. However within years, came the first reports of S. aureus strains that did not respond to methicillin. The incidence of methicillin-resistant S. aureus (MRSA) has increased greatly since, and it represents the major source of nosocomial infections. In 1980, synthetic fluoroquinolones were introduced to counter the threat of MRSA, but within a year 80% of isolated strains had developed resistance to these too. Vancomycin is regarded as a last-resort treatment for MRSA, for a number of reasons; it has a number of serious side-effects, its widespread use would encourage resistance against it, and it is extremely expensive. A case of vancomycin-resistant Staphylococcus aureus (VRSA) emerged in Japan in 1996; a few months later it had reached the USA. This represents a serious threat; some of these strains respond to treatment with a cocktail of antibiotics, but already people have died from untreatable VRSA infections [7].

MATERIAL AND METHOD

We have evaluated 291 samples collected from 278 patients hospitalized in ICU□s Clinical Emergency County Hospital Timişoara, in the period of March-June 2009. From 271 positive samples (bronchoalveolar fluids, wound secretions, urines, blood, peritoneal fluids, catheter tips) we isolated 276 microbial strains with nosocomial potential, from wich 69 were Staphylococcus aureus strains.

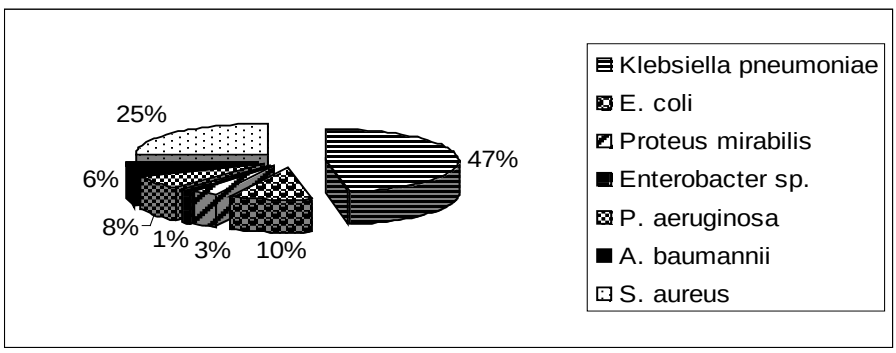
Isolation on culture media and identification of germs were performed at the level of hospital laboratory. Confirmation of identification tests, as well as extensive antimicrobial tests, were performed at the university laboratory. Identification was performed using PASTOREX STAPH PLUS kit (BioRad) and susceptibility tests, by disk diffusion tests (CLSI standards) with manual and automatic reading methods (Osiris-BioRad Laboratories). We used for testing the folowing drugs: penicillin, cefoxitine, amoxycillin+clavulanic acid, kanamycin, gentamicin, tobramycin, ciprofloxacin, erythromycin, clindamycin, linezolid, vancomycin, teicoplanin, tetracycline, fosfomycin trimethoprim-sulfamethoxazol and rifampicin were supplied by Bio-Rad.

RESULTS:

The objective of our study was to observe infectious status with methicillin resistant *S. aureus* (MRSA) in ICU.

We isolated 276 microbial strains with nosocomial potential (Fig. 1) and our attention focused on 69 *S. aureus* strains (25%). In five samples (3 bronchoalveolar fluids and 2 wound secretions) *S. aureus* was isolated in association with other microbial specimens: *Klebsiella pneumoniae* (bronchoalveolar fluids) and *Pseudomonas aeruginosa* (wound secretions).

Figure 1. Germs with nosocomial potential isolated from ICU



From 69 S. aureus strains, 30 strains were MRSA- (43,47%).

Table I. Resistance phenotypes in S. aureus strains

Resistance phenotypes	No.
PeniRMetiS+SXT	18
PeniRMetiS+MLSBi+SXT	12
PeniRMetiS+KTG+Q+SXT	9
MRSA+ MLSBc	4
MRSA+KTG+Q	4
MRSA+ MLSBi+KTG+Q	1
MRSA+ MLSBc+KTG	1
MRSA+ MLSBi+SXT	7
MRSA+ MLSBi+KTG+SXT	4
MRSA+ MLSBc+KTG+Q+SXT	9
TOTAL	**69**

Legend: PeniR- resistance to penicillin, MRSA- methicillin resistant S. aureus, MLSB- resistance to macrolide, lincosamide and streptogramin B, K- resistance to kanamycine, G- resistance to gentamycine, T- resistance to tobramycine, Q- resistance to quinolones, SXT- resistance to trimethoprim-sulphamethoxazole

DISCUSSIONS

- Methicillin acquired resistance develops by changes in antibiotic target. Alterations in penicillin binding proteins (PBPs) will offer resistance to all beta-lactam antibiotics [1, 2, 3].
- Our percent of MRSA (43,47%) is such as the percents of other European studies [5, 6]. The SENTRY study, which followed the epidemics of MRSA in 25 university hospitals across Europe, reported a percent of 25%, with variations between 2% (Utrecht, Holland) and 58% (Rome, Italy). In university hospitals from Europe included in the SENTRY study, the highest rate of MRSA was encountered in the Intensive Care Units, but only in a percent of 38%. On the other hand, the EPIC study, which has evaluated the frequence of MRSA in 1417 Intensive Care Units from 17 western-european countries, has reported a percent of 60% [4].
- In this study MRSA strains exhibit coresistance against the kanamycin, gentamicin, tobramycin, ciprofloxacin, erythromycin and trimethoprim-sulphamethoxazole.
- We did not isolate any strain with linezolid, vancomycin, teicoplanin, fosfomycin or rifampicin resistance. These remain the drugs of choice in serious staphylococcal infections.

CONCLUSIONS

1. In the Intensive Care Unit, Staphylococcus aureus was the second most frequent pathogen isolated, after Klebsiella pneumoniae.

2. The increased frequence of MRSA in the hospital enviroment explains the involvement of this pathogen in the etiology of nosocomial infections.

3. The methicillin-resistance of S. aureus was associated with other resistance mechanisms that determine inactivation of other antimicrobial classes.

4. The passive surveillance can be enough to control MRSA but not eradication.

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THE RENAL POLAR ARTERIES – ANATOMICAL CONSIDERATIONS

DĂESCU ECATERINA[1], JIANU ADELINA MARIA[1], MOTOC ANDREI[1], NICULESCU MARIUS CORNELIU[1], RUSU MUGUREL CONSTANTIN[2]

[1] Chair of Anatomy and Embryology, Victor Babeş University of Medicine and Pharmacy, Timişoara
[2] Discipline of Anatomy and Embryology, Chair MD 01, Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest

Correspondence to:
MC Rusu, Work Address: University of Medicine and Pharmacy "Carol Davila" 8, Bd.Eroilor Sanitari, RO-76241, Bucharest, Romania. Home Address: Str.Anastasie Panu 1, bloc A2, scara 2, etaj 1, apart.32, sector 3, RO-031161 Bucharest, Romania; Phone: +40722363705; E-mail: anatomon@gmail.com (M.C.Rusu)

ABSTRACT

The anatomy of the renal arterial variations is highly relevant for an adequate surgical performance. As renal arteries can enter the hilum or a renal pole, we consider these either hilar or polar, respectively. The later can present anatomical variations that we aimed to detail and classify by the present study, mainly designed as a qualitative one. We dissected the renal arteries on 56 human adult kidneys and we found in 12.5% superior polar arteries and in 8.9% inferior polar arteries. These were classified either as aortic or as renal, according to their origin from the abdominal aorta and the renal artery. A single specimen presented an inferior polar artery originating the gonadal artery, on the left side. According to our results we consider that polar arteries may be classified either as solitary or pedicular: accompanied by a polar vein and a ganglionated nerve plexus. Also, a polar artery may be of type I (false supernumerary) if it replaces a segmental artery or of type II (true supernumerary) if the respective segmental artery emerges the renal artery.

Key words: kidney; renal artery; gonadal artery; renal segments.

INTRODUCTION

The anatomy of the renal arterial variations is highly relevant for an adequate surgical performance [Satyapal et.al., 2001, Rao et.al., 2006, Gesase, 2007, Shakeri et.al., 2007]. Variations of the renal arteries may influences urological, renal transplantation and laparoscopic surgeries [Shakeri et.al., 2007]. The renal artery (RA) originates as a lateral, paired branch of the abdominal aorta. The standard textbook description of the renal vasculature as consisting of an artery and a vein occurs in less than 25% of cases [Ciçekcibaşi et.al., 2005]. There is non-conformity in the literature regarding the nomenclature and incidence of additional renal arteries, that have been variously described as "accessory", "aberrant", "anomalous" and "supernumerary", "supplementary", "multiple", "accessory aortic hilar", "aortic

superior polar", and "aortic inferior polar". "upper polar" and "lower polar". As so, there exists an obvious need for the nomenclature to be standardized to facilitate reporting of the incidence of additional renal arteries [Satyapal et.al., 2001]. As renal arteries can enter the hilum or one of the renal poles, superior and/or inferior, we consider these either as hilar or, respectively, as polar arteries. The later can present anatomical variations, of origin, topographical and related to the vascularized renal parenchyma that we aimed to detail and classify by the present study. The present study was mainly designed as a qualitative one.

MATERIALS AND METHODS

For the present study we dissected a total lot of 56 human adult kidneys. 34 were dissected free in autopsy, when the origins of the arteries were recorded, and then the renal arterial system was evaluated by dissection of the respective fixed in formalin specimens. 22 kidneys were dissected in situ during the educational process in the anatomy rooms of the authors' institutions. The polar arteries were recorded for the origin, topography and distribution. Moreover, the respective kidneys were divided in frontal planes in order to identify the segmental arterial pattern and to correlate it with the intraparenchymal distribution of the polar arteries.

Abbreviations

RA – renal artery;
RV – renal vein;
PST – presegmentary trunk;
SA – segmentary artery;
LA – lobar artery;
Ao – aorta;
ICV – inferior cava vein;
SPA – superior polar artery;
IPA – inferior polar artery;
IMA – inferior mesenteric artery.

RESULTS

In 5 specimens (12.5%) we encountered superior polar arteries (SPAs) and in 7 different specimens (8.9%) we found inferior polar arteries (IPAs). We classified the SPAs as aortic if these originated from the abdominal aorta (2 kidneys from different donors, 3.5%) and as renal if these emerged from the main trunk of the renal artery (2 left and 1 right kidneys, in different donor cadavers, 5.3%). The IPAs had aortic origins (fig.1) in 6 specimens (10.7%) and one specimen (fig.2) presented one IPA originating the left gonadal artery (1.7%) and so, coursing in front of the ureter (the respective gonadal artery left the aorta and was anatomically and topographically normal). One aortic SPA we identified entered the superior renal pole alone and it supplied the superior pole of the respective kidney together with an apical branch emerged from the posterior segmental artery. The other aortic SPA was the only supplier of the superior (apical) segment of that kidney. One of the renal SPAs we identified entered the superior renal pole within a superior polar pedicle, together with a superior polar vein and a microganglionated neural plexus (fig.3) and to the parenchyma of the respective superior (apical) segment also a superior (apical) segmental artery (of the anterior group of segmental arteries) was also distributed. The other two renal SPAs identified were the only suppliers of the respective superior (apical) renal segment (fig.4). All the IPAs we encountered added within the inferior renal segment to inferior segmental arteries originating with various patterns from the RA.

DISCUSSION

In what concerns the possible origin of renal polar arteries our results correlate with indexed references: aortic polar arteries were reported by Gesase (2007) and Shakeri et.al. (2007) while renal polar arteries were reported by Rao et.al. (2006) and Shakeri et.al. (2007). Gesase (2007) also reported an IPA originating the inferior

mesenteric artery and constituting a polar vascular pedicle together with an accompanying vein. Taking this into account and considering that we also found a SPA constituting a neurovascular and not only vascular bundle we must emphasize that the polar arteries of the kidneys may be classified either as solitary or pedicular and these types must be identified by the surgeon even if the polar artery was identified by an imagistic method prior to the intervention (a patient positive for a polar artery isn't surely negative for an accompanying vein).

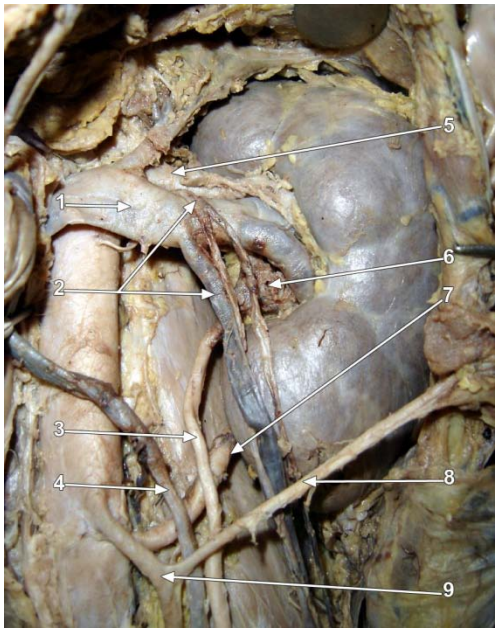

Fig. 1 – IPA with aortic origin, at the level of the origin of the inferior mesenteric artery. Left side, anterior view. 1.renal vein; 2.gonadal vessels; 3.ureter; 4.inferior mesenteric vein; 5.renal artery; 6.renal pelvis; 7.IPA; 8.left colic artery; 9.inferior mesenteric artery.

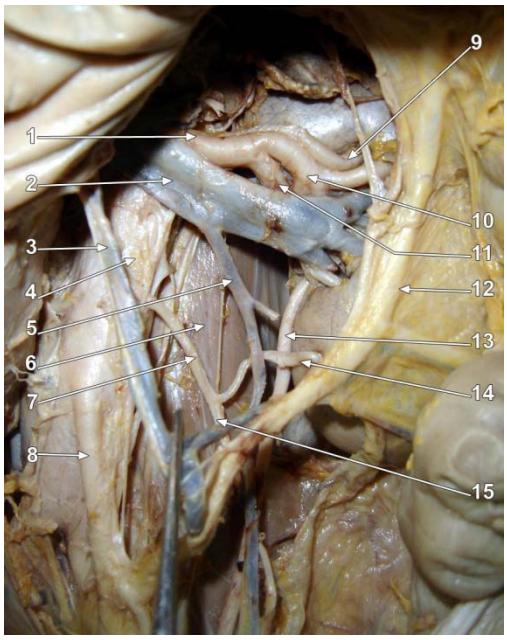

Fig. 2 – IPA leaving the left gonadal artery. 1.renal artery; 2.renal vein; 3.inferior mesenteric vein; 4.aorta; 5.gonadal vein; 6.greater psoas muscle; 7.gonadal artery; 8.inferior mesenteric artery; 9.superior segmental artery; 10.common trunk of the anterior superior, anterior inferior and inferior segmental arteries; 11.posterior segmental artery; 12.left colic artery; 13.ureter; 14.IPA; 15.gonadal artery, continued distally to the IPA.

Bordei et.al. (2004) found, when studying a selected lot of 54 kidneys with double renal arteries, SPAs in 5 cases, IPAs in 16 cases and they also found in other 5 cases supplementary renal arteries dividing each into a polar and a hilar branch. We didn't encounter the later morphology described by Bordei and also our frequencies differ of them if we also take into account that we worked on an unselected lot. But one must consider also the hazard of samples and the fact that the main relevance for surgeons still remains the morphology and topography of such polar arteries. Ciçekcibaşi et.al. (2005) considered that such polar arteries should be named multiple arteries since these vessels are in fact normal segmental end-arteries, without anastomoses between them and so, these vessels correspond indeed to the segmental branches of a single RA. According to the anatomic nomenclature, the kidney is divided in 5 segments, 4 anterior and 1 posterior [Feneis et.al., 2000], the anatomical superior segment usually and constantly being described as apical by the surgeons that agreed to the terms of Graves (1954). As so,

in the opinion of these authors, a polar artery only substitutes a superior/apical or an inferior segmental artery. From our study resulted two general patterns of distribution of a polar artery that come in opposition with the hypothesis of Ciçekcibaşi and coworkers. The respective patterns we defined are:

– type I – polar artery as a substitute of the respective, superior/apical or inferior segmental artery, so an unique artery of the respective segment of the kidney;
– type II – polar artery as an additional supplier of the respective renal segment, in the presence of the segmental artery.

Fig. 3 – Superior polar pedicle (a:artery, v:vein, gg:microganglion of the periarterial neural plexus) of the left kidney, posterior view. 1.renal artery; 2.posterior segmental artery; 3.renal vein; 4.renal pelvis; 5.ureter.

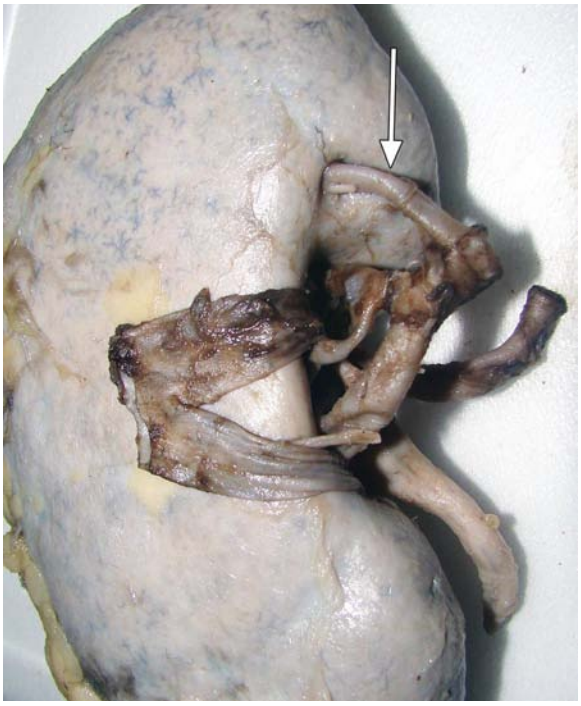

Fig. 4 – Right renal SPA (arrow), anterior view.

As so, we consider that the type I polar arteries can be considered false supranumerary arteries while the type II polar arteries we defined can be viewed as real supranumerary arteries of that kidney. This appears highly relevant for segmental nephrectomies, especially when type II polar arteries are eoncountered and ligated as unique arterial resources of that renal segment, because undesired bleeding will result. An IPA crossing the ureteropelvic junction, as we identified, can be the cause of obstruction and pelvicalyceal dilation [Shoja et.al., 2008]. There are studies describing the origin of a gonadal artery from a renal artery, hilar or polar [Shoja et.al., 2007]. We presented here a case with an IPA originating the gonadal artery. Our evidence comes to sustain the supposition of Shoja et.al. (2007), for a common embryonic error that occurred in the formation of accessory renal and aberrant gonadal arteries.

CONCLUSION

Even though the polar arteries of the kidney can be viewed as generally known, one must take into account their possible presence in polar pedicles and not solitary

and also their distribution to that renal segment as fals or true supranumerary arteries.

Acknowledgements
To Professor Virgiliu Niculescu.

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DEEP NECK INFECTION – CASES PRESENTATION AND REVIEW OF THE LITERATURE

M. PRICOP[1], Ş. TALPOŞ[1], H. URECHESCU[1]

[1] University of Medicine and Pharmacy "Victor Babeş" Timişoara

Correspondence to:
Marius Pricop, Spl. Nistrului nr. 7, 300093, Timisoara, Romania, phone: 0040256436085, email: pricopmarius@yahoo.com

ABSTRACT

Despite the use of antibiotics, infections of the deep spaces of the neck continue to have the potential for serious and even life threating complication.

Delay in diagnosis or worse, a missed diagnosis, can lead to severe consequences incuding mediastinitis and death.

The aim is to intervene aggressively, both medically and surgically, prior to the onset of complications.

Once abscess formation occurs, surgery is still considered the main treatment.

Key words: neck infection, complications, abcess, sugery, treatment.

INTRODUCTION

Frequency

No accurate estimate of the frequency of deep neck space infections worldwide presently exists. The complication rate is also likely to be greater in areas without wide access to modern medical treatment (antibiotics, imaging modalities, intensive care support).

Etiology

Before the widespread use of antibiotics, 70% of deep neck space infections were caused by spread from tonsillar and pharyngeal infections. Today, tonsillitis remains the most common etiology of deep neck space infections in children, whereas odontogenic origin is the most common etiology in adults.

The main causes of deep neck infections include the following: tonsillar and pharyngeal infections, dental infections, oral surgical procedures, salivary gland infection or obstruction, trauma to the oral cavity and pharynx, foreign body aspiration, cervical lymphadenitis.

As many as 20-50% of deep neck infections have no identifiable source.

Pathophysiology

Deep neck space infections can arise from a multitude of causes. Development of a deep neck space infection proceeds by one of several paths, as follows:

Spread of infection can be from the oral cavity, face, or superficial neck to the deep neck space via the lymphatic system.

Lymphadenopathy may lead to suppuration and finally focal abscess formation. Infection can spread among the deep neck spaces by the paths of communication between spaces.

Direct infection may occur by penetrating trauma.

Microbiology

The microbiology of deep neck infections usually reveals mixed aerobic and anaerobic organisms, often with a predominance of oral flora. Both gram-positive and gram-negative organisms may be cultured.

Group A beta-hemolytic streptococcal species (Streptococcus pyogenes), alpha-hemolytic streptococcal species (Streptococcus viridans, Streptococcus pneumoniae), Staphylococcus aureus, Fusobacterium nucleatum, Bacteroides melaninogenicus, Bacteroides oralis, and Spirochaeta, Peptostreptococcus, and Neisseria species often are found together in various combinations.

Pseudomonas species, Escherichia coli, and Haemophilus influenzae are occasionally encountered.

Presentation

Obtain a detailed history from patients in whom deep neck space infection is suspected. A history of the following is important: pain, recent dental procedures, neck or oral cavity trauma, respiratory difficulties, dysphagia, immunocompromised status.

Physical examination should focus on determining the location of the infection, the deep neck spaces involved, and any potential functional compromise or complications that may be developing.

A comprehensive head and neck examination should be performed, including examination of the dentition and tonsils. The most consistent signs of a deep neck space infection are fever, elevated WBC count, and tenderness.

Other signs and symptoms: Asymmetry of the neck and associated neck masses or lymphadenopathy; Medial displacement of the lateral pharyngeal wall and tonsil; Trismus caused by inflammation of the pterygoid muscles; Torticollis and decreased range of motion of the neck caused by inflammation of the paraspinal muscles;

Fluctuance that may not be palpable because of the deep location and the extensive overlying soft tissue and muscles (eg, sternocleidomastoid muscle);

Possible neural deficits, particularly of the cranial nerves (eg, hoarseness from true vocal cord paralysis with carotid sheath and vagal involvement), and Horner syndrome from involvement of the cervical sympathetic chain;

Tachypnea and shortness of breath (may suggest pulmonary complications and warn of impending airway obstruction).

Laboratory Studies

The following tests may be useful for the patient in whom a deep neck space infection is suspected: blood chemistries, complete blood cell count, clotting profile, blood cultures (may be indicated in septic patients), abscess cultures with Gram stains.

Imaging Studies

The following imaging studies may be useful: mandible series (Panoramic radiography), chest radiography, CT scanning, MRI.

Medical Therapy

Airway; The airway is the first priority of treatment. Addressing the airway may involve observation, endotracheal or nasotracheal intubation, tracheostomy for emergent situations.

Even in experienced hands, attempted oral or nasal endotracheal intubation in a patient with a deep neck space infection or abscess may be extremely difficult. The potential exists for abscess rupture with intubation leading to aspiration, acute airway obstruction, or death.

Other factors (eg, tracheal deviation, external airway compression, trismus, cervical spine rigidity) can produce difficulty with intubation.

Patients presenting with respiratory distress should undergo a tracheostomy while under local anesthesia to secure a safe airway.

A tracheostomy is safer, more conservative, and preferable to the development of respiratory compromise, and should be performed before any attempts at surgical drainage in these patients.

Cultures

Obtain cultures whenever possible to help direct antimicrobial therapy.

This may involve cultures of the neck, abscess fluid, and blood. Volume and metabolic resuscitation. Initiate these procedures in all patients with deep neck infection. Identify and address metabolic derangements during resuscitation. Address attention to other concurrent medical problems (eg, diabetes) early in the course of treatment.

Intravenous antibiotics. Choose parenteral antibiotics to cover the most likely organisms. Initiate empiric regimens before culture results are obtained based on the local resistance patterns and most common etiologies. Modify antibiotics according to culture and sensitivity results. Clindamycin and ampicillin/sulbactam are currently the most used antibiotics.

Surgical therapy

Incision and drainage. Incision and drainage is the treatment of deep neck space abscesses. Establish a secure airway before initiating any surgical procedure.

Perform incision and drainage in patients with no improvement after 48 hours of I.V. antibiotics. Many approaches are possible to the deep neck spaces. Every approach used must ensure adequate exposure and access to allow drainage without compromising surrounding structures. Abscess cavities should be copiously irrigated, débrided, and left open with a drain or packing to prevent reaccumulation. Once an abscess has been entered, cultures should be obtained to help direct antimicrobial therapy.

Complications

Deep neck infections have many severe life-threatening potential complications:

- Airway obstruction from compression of the trachea
- Aspiration (may occur spontaneously or during endotracheal intubation)
- Vascular complications (ie, thrombosis of the internal jugular vein, carotid artery erosion and rupture)
- Mediastinitis from inferior spread along fascial lines
- Neurologic deficits
- Septic emboli
- Septic shock
- Necrotizing cervical fasciitis
- Osteomyelitis due to local spread to bones of the spine, mandible, or skull base

Several studies have looked at factors that may cause an increase in the risk of complications from deep neck space infections. One study by Wang et al found a higher risk of complications in females, patients with neck swelling, and patients with associated respiratory symptoms.

Another study by Huang et al suggests that diabetes and the presence of other underlying systemic diseases significantly increases the risk of complications.

Outcome and Prognosis

Patients treated for deep neck infections can be expected to fully recover as long as the infection is treated properly and in a timely manner.

Patients whose treatment is delayed can expect a greater number of complications and a prolonged course of recovery. Once a deep neck infection has fully resolved, no particular predisposition exists for recurrence.

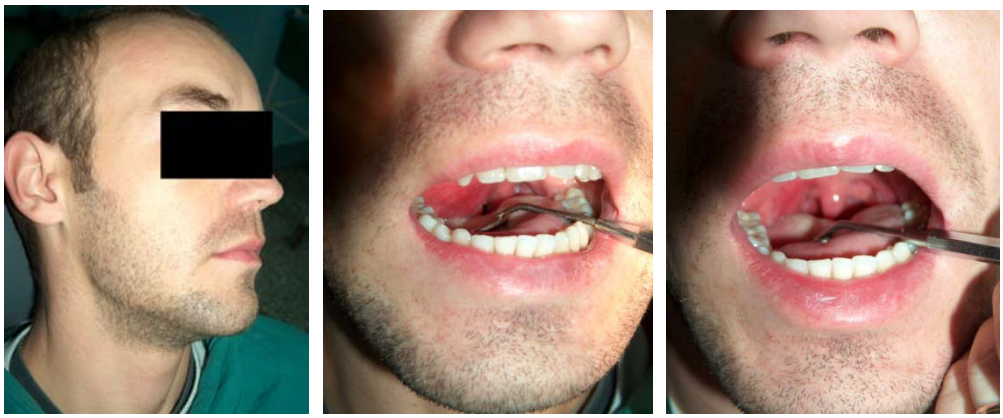
CASES PRESENTATION

Case 1

Left laterofaringian abscess: no etiology found, treatment: incision, antibiotic (clindamycin) and drug therapy, resolution in 10 days.

Case 2

Right laterofaringian abscess: etiology - 37 periapical granuloma, treatment: incision, antibiotic (amoxycilline) and drug therapy, resolution in 6 days.



Case 3

Right laterofaringian abscess: etiology - 48 periapical granuloma, treatment: incision, antibiotic (clindamycin) and drug therapy, resolution in 12 days.

CONCLUSIONS

Deep neck infections, although less common than in the preantibiotic era, are still present. Antibiotic therapy has changed due to new resistance patterns of the bacteria causing deep neck infection. CT and MRI are the imaging studies of choice, as they can demonstrate abscess location and help to differentiate cellulitis from abscess. It should be remembered that deep neck abscesses may cause severe complications, and that surgical treatment and close monitoring of patients with these infections is essential.

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PAGES 23-27

MICROIMPLANT ANCHORAGE IN ORTHODONTICS

BORDEI ANCA GEORGIANA[1] , DRAGOŞ STANCIU[2]

[1] Phd student, Department of Orthodontics, Faculty of Dentistry, University of Medicine and Pharmacy „Carol Davila" Bucureşti
[2] Prof. Dr., Head of Orthodontics Department, Faculty of Dentistry, University of Medicine and Pharmacy „Carol Davila" Bucureşti

Correspondence to:
Bordei Anca Georgiana, geo_nicola@yahoo.com

ABSTRACT

The control of anchorage is one of the most critical factors in orthodontic treatment. The reinforcement of an anchorage usually needs a complicate biomechanics and a patient compliance. Also, there are many times when absolute anchorage is needed. But, considering Newton's Third Law, it is virtually impossible to achieve absolute anchorage condition in which reaction force producing no movement at all, especially with intraoral anchorage. Thus extraoral anchorage, such as head gear, is traditionally used to reinforce anchorage. However, the use of extraoral anchorage demands full cooperation of patient as well as 24 hours of continues wear which cannot be done. Therefore, it is extremely difficult to attain excellent result without compromising treatment in some way.Therefore, to treat patients without patients' compliance, clinicians and researchers have tried to use skeletal anchorage. Gainsforth and Higley(1945) placed metallic vitallium screws in dog ramus as anchors and applied elastics to the maxillary arch wire for distalization of maxillary dentition as long ago as 1945. However, all screws were failed within one month.

After Brånemark and co-workers reported successful osseointegration of prosthodontic implants in bone, osseointegrated implants have been used as intraoral orthodontic anchorage, but their usage has many limitations for routine orthodontic practice.

Key words: orthodontic treatment, microimplant, anchorage, micro-screws, tooth movement, skeletal anchorage system.

INTRODUCTION

Since 1998, Park & Bae (Park, 1999; Park et al, 2001; Bae et al, 2002; Bae et al, 2002) have started to use surgical micro-screws (1.2mm in diameter) to retract anterior teeth after placing them between the roots of upper 2nd premolars and 1st molars. It was very successful without any complications. Kyung et al (2003) developed orthodontic Microimplant (Absoanchor○R), which has been designed specifically for orthodontic purpose and has a button-like head with a small hole. Also, by giving inclination on cervical area of the button allows natural separation of elastomers from gingiva. A hole is made in upper structure for smooth application of elastomer such as elastomeric thread and/or ligature wire. This newly designed microimplant has helped to solve the main objections to previous implants and surgical screws (Sung et al, 2006). We

designed several sizes of diameter from 1.2 mm to 2.7 mm of micro-implants with different types of head for different tasks and sites. However, many orthodontists are still hesitating to use orthodontic microimplants, because many of them are afraid of surgical intervention and post-surgical complications. But unlike prosthetic implants, there is little complication, and every dentist including orthodontist can insert orthodontic microimplants.

Terms used in skeletal anchorage. There are many terms used in orthodontic skeletal anchorage, such as, skeletal anchorage system, mini-screw, micro-screw, mini-implant, micro-implant, mini-screw implant, micro-screw implant, Temporary Anchorge Device(TAD) etc. Academically the term of micro- is used more rather than mini-, for example, micrognathia, microglossia, microdontia, etc. Also, implantologists already used the term mini-implant, which is a kind of temporary implant to make temporary crown during osseointegration of implant. Every orthodontic implant has screw portion. For the same reason, we don't need to put the term screw, such as micro-screw implant. Therefore, we prefer to use the term microimplant for orthodontic screws.

Types of Absoanchor R Microimplants

Several types of Absoanchor microimplants are available for different tasks and sites. Different types of head structures can be chosen depending on kinds of elastomers, biomechanics, sites of placement and individual preference etc.

Fig.1.1 Several types of Absoanchor microimplants are available for different tasks and sites. Different types of head structures can be chosen depending on kinds of elastomers, biomechanics, sites of placement and individual preference etc.

Selection of microimplants

1) Depending on the length; The length of screw portion is ranging from 5mm to 12 mm. Longer microimplants lead to better mechanical stability like dental prosthetic implants, but more possibilities of invading adjacent anatomical structures, such as roots, maxillary sinus and nerve etc. According to our clinical experiences, 6mm of screw depth is enough for maxillary bone, and 5mm is enough for the

mandible. However, always we should consider the depth of soft tissue when choosing proper length of microimplantsd. Especially palatal mucosa may be very thick in many. So, if soft tissue is 6mm thick, in order to place 6mm of screw portion into the bone, at least 12mm length of microimplant should be chosen. This protocol requires that the soft tissue thickness as well as the bone quality must be evaluated at the location of placement. Also, in choosing the proper length of a microimplant, the path of insertion of the microimplant must be considered. A microimplant can be placed either in a diagonal direction or a perpendicular direction relative to the cortical bone surface. It is better and easier to place microimplant in a perpendicular direction, but, there are many situations in which the microimplant should be placed in a diagonal direction so as to avoid injury to an adjacent tooth root. When the microimplant is placed in a diagonal direction rather than perpendicular direction, it is better to use a slightly longer microimplant.

2) Depending on the diameter; There are various diameters of Absoanchor microimplants which are ranging from 1.2 mm to 2.7 mm, so they can be placed anywhere in the mouth. Depending on the inter-radicular distance, quality of bone and site of placement, we can choose different diameters of microimplants. Thicker the microimplant, the greater becomes mechanical retention, but also the greater possibility for root contact. Followings are general tips for selecting proper diameter of microimplants depending on the inserting sites;

a) buccal & labial areas of maxilla : Cortical bone in these areas is not that thick, so use tapered microimplant neck of 1.3-1.4mm and tip of 1.2-1.3mm thick. Microimplants made by titanium alloys of this thickness can be inserted safely without pre-drilling on maxillary buccal areas.
b) palatal areas of maxilla : Soft tissue is thick, so usually microimplants of longer than 10mm is needed, but the longer, the higher possibility of breakage, so use a little thicker ones (1.5-1.6 mm of neck) than buccal areas. The distance between roots is greater in palatal areas than buccal area, there is lower possibility of root contact even when using thicker microimplants.
c) midpalatal suture : There is no worries for root contact, and also this is sutured area, so thicker ones are used. Microimplants of diameter larger than 1.7mm is recommended. Even 2.7mm thick one can be used for younger cases.
d) buccal & labial areas of mandible : Cortical bone of mandible is harder than maxilla, so, a little thicker ones (1.4-1.6mm) are better to prevent breakage especially for self-drilling (drill-free) method.

5. Surgical procedures of microimplant installation

a) Local Anesthesia. Local anesthesia is only needed to the site to be inserted, and less than 1/4 dental lidocaine ample per site is enough. Sometimes, only topical anesthesia is enough to insert on the attached gingival area. The effect of anesthesia does not need to be deep, only soft tissue and periosteum should be anesthesized.
b) Pilot Drilling. When using drill-free method ,microimplant of small diameter is likely to be broken when alveolar bone is too hard. Therefore microimplant is safely installed by pre-drilling method especially on adults' mandibular areas. You may drill only through cortical bone to

prevent fracture. However, it's better drill up to the length of microimplant to install. To reduce heat production, drilling speed should be around 500-1000rpm, and rotate intermittently with normal saline irrigation.

c)Microimplant driving. Microimplant driving methods can be divided into pre-drilling (self-tapping) method and drill-free (self-drilling) method. When we drill in advance, we can insert microimplant to the direction of drill. However most people feel drilling is annoying, so favor drill-free method. Most microimplants in the market are made of strong titanium alloys, not of a little pure titanium, so even diameter of 1.2mm-1.3mm may be inserted without drilling. However since hardness of alveolar bone varies with the persons and the sites, if we feel a little heavy resistance when driving microimplants by drill-free method, we should remove the microimplants and change to pre-drilling method. We may use engine driven method to insert microimplant, using speed reduction contra angle like prosthetic implants, but this may lead to more possibility of microimplant breakage, thus it is safer to use hand driver to feel resistance of microimplant driving torque. We should never give excessive force, because if microimplant is broken during driving, it may be a little troublesome to remove.

d) Special attention after inserting microimplants. Although good early fixation is achieved, inflammation should lead microimplant to be movable and loosened. Therefore to prevent inflammation, implanted site should be always keep clean by water irrigation or soft toothbrush. Also patients should be warned not to touch microimplant by their fingers. Antibiotics prescription is not necessary with microimplant installation without incision. Also analgesics are not necessary, for microimplant of small diameter rarely induces pain or swelling. However patients should be told to revisit the clinic when feeling pain during mastication. This kind of pain is usually derived form contact with root, so if diagnosed to root contact, you should move teeth away from microimplant. If you feel slight mobility, you may rather retighten microimplant, not remove it.

e)Explanation for possibility of failure. Microimplant has a failure rate of 5~25% depending on the dentists' technique, patients' type, insertion sites, and usually more failure occurs on mandible rather than maxilla. The patients should be fully noticed with the possibility of failure before starting microimplants.

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ACUTE CORONARY SYNDROME –PRE (POST)-HOSPITAL TRIAGE IMPORTANCE

REDNIC MEDA IOANA[1], COBZARIU I.F.[2], VELIMIROVICI DANA[2], RADA MARIA[2], SARĂU C.A.[2], DRĂGAN SIMONA[2]

[1] MD, resident for familly medicine, Medical Emergency atestat, CPU coordonator, Hospital: Mun. Sighetu-Marmaţiei;
[2] Clinical and Medical Emergency Department, Univercity of Medicine and Pharmacy „Victor Babeş" Timişoara

Correspondence to:
Rednic Meda Ioana, tel.: 0745634595, e-mail: rmioana@yahoo.com

ABSTRACT

The incidence of acute coronary syndrome is very high in our country. Its evolution is often severe and mortality is still very high. The intention of our study is part of general efforts to detect opportunities for improvement in morbidity and mortality due to myocardial ischemia. In this article, we present modern action guidelines for each phase of the ACS corresponding to each step of emergency care and attitude from the immediate pre-hospital therapy and ending with various methods of coronary reperfusion. Submit a personal study conducted in assessing the significance and importance of pre-hospital triage for correct diagnosis of ACS and effective guidance caronarian acute attack victims to appropriate services for proper coronary desobstruction. The conclusion is that early pre-hospital triage has the advantage to employment in "golden time" for different methods of myocardial reperfusion.

Key words: ACS, in pre-hospital triage, coronary reperfusion, gold hour.

INTRODUCTION

Considering the recommendations from the „ACC/AHA Guideline for the Management of patients With ST-Segment Elevation Myocardial Infarction",Eugene Braumwald, 2004 Update, Elliott Antman, the natural history of coronary artery disease and the evolution to the major acute coronary syndromes, are the folowing:

a) Unstable plaque. Rupture of a lipid-laden plaque with a thin cap is the usual cause of an acute coronary syndrome (ACS). The majority of these plaques are not hemodynamically significant before rupture. An inflamatory component in the subendothelial area further weakens and predisposes the plaque to rupture. Speed of blood flow, turbulence, and vessel anathomy may also be important contributing factors. Superficial erosion of a plaque and other causes accur in a minority of patients.
b) Plaque rupture. After rupture, a monolayer of platelets covers the surface of the ruptured plaque –

platelet adhesion. The rupture attracts and activates additional platelets – platelet aggregation. Fibrinogen cross-links platelets and the coagulation system is activated, with thrombin generation.

a) Unstable angina. A partially occluding thrombus produces symptoms of ischemia, which are prolonged and may accur at rest. At this stage, the thrombus is platelet-rich. Therapy with antiplatelet agents such as aspirin, clopidogrel and GP IIb/IIIa receptor inhibitors is most affective at this time (!!!). Fibrinolytic therapy is not effective and may paradoxically accelerate occlusion by the release of clot-bound thrombin, which promotes coagulation. An intermittently occlusive thrombus may cause myocardial necrosis, producing a NSTEMI.
b) Microemboli. As the clot enlarges, microemboli may originate from the thrombus and lodge in the coronary microvasculature, causing small elevations of cardiac troponins, the sensitive cardiac markers. These patients are at highest risc for progresion to MI. This process is known as minimal myocardial damage.
c) Occlusive thrombus. If the thrombus occludes the coronary vessel for a prolonged period, a STEMI usually occurs. This clot is rich in thrombin. Early and prompt fibrinolysis or direct percutaneous coronary intervention (PCI) may limit infarct size (if performed sufficiently early).

Once again, for the victim's benefit is necesary to have a promptly therapeutic atitude and a suitable medical treatment (but not a very promptly fibrinolytic therapy!).

What we have to do?

For the first time we have to do an IMMEDIATE ASSESMENT – <10 minutes:

a) at patient's home (or in the ambulance):evidence of the vital signs: pulse, respiration, blud presure; perform brief, targeted history of the present symptoms; physical exam; oxygen saturation; intravenous access
b) in the emergency departament (because in our country is not yet possible to make this in the ambulance): 12-lead ECG, chest x-ray (< 30 minutes, if possible), initial serum cardiac markers levels, initial electrolyte and coagulation studies.

In the same time, we have to give IMMEDIATE GENERAL TREATMENT: Oxygen at 4-6 L/min, Aspirin 300 mg, Nitroglycerin 5-10 mg SL or spray, Antalgic IV (Algocalmin, Piafen, Fortral) (if pain not relieved with nitroglycerin), β-Adrenoceptor blockers IV (to forewarn the cardiac disrithmias). (N.B. Memory aid: „OANA- β" greets all patients.)

Emergency medical sistems personnel must can to perform immediate assesment and treatment (OANA- β), including initial 12-lead ECG and review for reperfusion therapy indications and contraindications. World wide, the management of prehospital medical asistance in emergency situations, recognise the folowing steps:

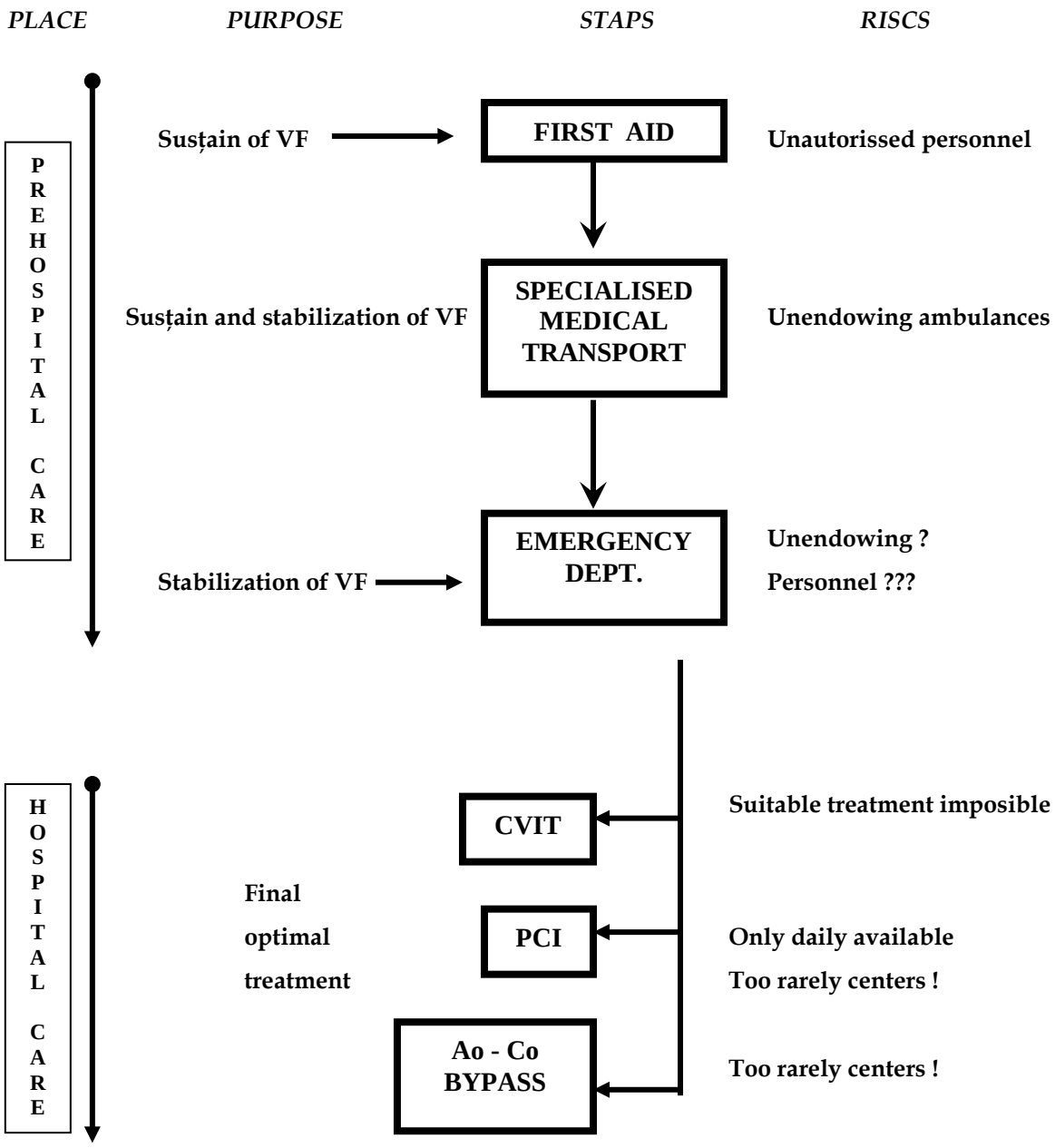
1.- first aid,

2.- the emergency asistence during the specialised medical transport and,

3.- the emergency medical asistence in the emergency departament (ED).

I'l present you the steps of the emergency cardiovascular care in prehospital area, particulary for the ACS victims: (Figure 1.1).

The managerial algoritm of the emergency medical asistence for ACS:



Legend: CVIT – cardiovascular intensive therapy; PCI - percutaneous coronary intervention; Ao-Co By-pass – aorto-coronarian by-pass.

In Romania, today, we have the posibility to ensure the first aid step if, the emergency medical sistems (EMS) personnel, is present to the scene of onset the ACS, so quicly as possible. Because of less of medical education, one victim of the ACS onset has not another possibility to recive the right treatment and emergency atitude (f.e. from the family medical assitence). It's real that, the first aid, in ACS Cass (the suitable treatment), can be selftaken too! But, for that, we need also to promote the medical and sanitary education. (In the present articol I'l presents you the results of a sociologycal study about the subject: medical and sanitary education.) There ware also necessary, for the time economy and the patients benefit, that the ambulances have been endowing with electrocardiografs for

12-lead ECG. The personnel who work in the Districtual Ambulance Servicies must know to perform the 12-lead ECG. Unfortunately, the reality, is steel another one. Another very seriously problem is the time waste. For the personnel working on ambulances, it is often impossible to recognise the ACS right form and the right particular treatment too. In these Casses it is imposible to give the patient the right treatment and to bring him/her directly to the optimal hospital. Actually, the personnel of the ambulance has not another possibility that to bring the subject to the apropiate (general) emergency departament. Here are macking the first doubtless ECG diagnostic and the first paraclinic invetigations (initial serum cardiac markers levels, and initial electrolyte and coagulation studies). After all of that, hardly, the subject receives the right general treatment or the specific treatment (f.e. fibrinolytic therapy) or, if the PCI is the treatment of choice, the patient must to be transfered to a hospital where the PCI is available. But, we know that these cardiovascular centers are very rarely and PCI is only during the day available. Fibrinolysis treatment (FT) is known as an excellent method for coronary repermeabilisation but "timing" professional identification of acute coronary attack, unable to recognize early indications of the fibrinolytic therapy, high variability and the presence of freqvent fibrinolysis contraindications, absence of the prehospital triage, determining in many cases the loss of " Golden Time "- two hours - and postpone risky and complicated fibrinolytic repermebilisation. Eighth decade of the twentieth century marked the beginning for percutaneous coronary intervention (PCI) in acute coronary syndrome. Today, percutaneous coronary intervention in acute coronary syndrome, expresses the ability of synthesis of knowledge of physiology - pathophysiology and morphology - morphopathology on cardiovascular hemodynamics, symbiosis infarction - coronary circulation and, on myocardial ischemia and necrosis process it. Interventional gesture importance increases with the realization that, acute coronary syndrome and myocardial infarction was, is and will remain a major emergency that prevails in mortality for cardiovascular and overall mortality. There were many controversies still exist about the usefulness and use of late PCI in old coronary occlusions beyond the optimum of 6-12 hours after onset. Evidence from increasing real and full benefits for desobstruction, even belatedly, by saving large areas of myocardial necrosis zone around itself, resulting in preventing aneurysm remodeling type and limit the expansion chamber of the left ventricol, led to the crystallization and even strengthening the most actual theories and practical attitude to influence the morbidity and mortality in ACS and acute myocardial infarction: the theory of "open vessel". According to this theory, any patent coronary artery (after occlusion not older than 3-6 months and sometimes even later if it can be documented myocardial viability), is more useful than an irreversible closed artery through phenomena such as: improving coronary collateral circulation, turgidity perinecrotic area by revascularization, intramyocardic arterio-venous system improvement, etc. Ischemic preconditioned myocardium (hibernating) and nurtured by vascular collaterals, survives as the form of "sideral myocardium", even after a complete occlusion, can thus be revived to life, means active contraction after some time, doing the responsible vessel desobstruction. That some time, may be between a few minutes and a few months. Remains the optimal coronary dezobstruction practiced the first six hours (more than twelwe hours - after the last study) from the onset of acute coronary event. The ideational and practical new approach, alowed once again, for the first time in modern cardiology, effective and impressive decline in mortality from inhospital acute myocardial infarction, under 7-8%, a percentage available today. Therefore we try to conclude that, always disputed competition between the three

modern methods of myocardial revascularization: thrombolysis, PCI and bypass aorto-coronary, has the current leadership, the PCI procedure.

Here would be the terms of a comparison: Thrombolysis has the great advantage of the drug could be available in all territorial health units but is encumbered by a higher rate of failure and lack of thrombolytic medication in the prehospital medical emergency care.

Primary PCI in ACS and acute myocardial infarction, has a success rate of 90-95% by achieving optimal repermeabilisation, vascular caliber near an ideal, especially when conducted in the first 6-9-12 hours of the ischemic attack onset. An optimal vascular repermeabilisation results in poststenotic coronary blood flow as closely as TIMI grade III.

TIMI study documented the famous classification is as follows:

TIMI 0 = vessel blocked (closed);
TIMI I = flow late and only partially;
TIMI II = slightly delayed;
TIMI III = normal flow (optimal).

Moreover, early postinterventional occlusion rate is much smaller for PCI - only 1-2%; residual stenosis after thrombolysis drug (GUSTO I study), is practically absent in PCI and bleeding complications of thrombolysis are nonexistent PCI practice. At the same time, PCI has the advantage - from revascularization surgery (bypass aorto-coronary), but this time - to be less invasive, fewer complications encumbered and less disabling and a lower intra- and postoperative mortality. We add and economic references in this "competition" overall costs are lower ICP by decreasing length of hospitalization and medication costs required. Are not neglected aspects of patient comfort - considerably more if PCI practice - and those related to reducing the period of temporary disability for people in work activity. There are, of course, disadvantages of percutaneous coronary intervention. Postintervenional restenosis phenomenon, imposed further PCI procedures. But this is controllable by the same method and presents a rare dramatic face. From a sociological study, carried out by our team, follows a major role award in the attitude of pre-hospital and posthospital triage, for acute coronary events. The "triage" attitude, we understand a professionalising correct and early diagnosis of acute coronary attack, followed the by orientation and delivery of victims directly in a hospital unit equipped with material and human resources optimally assigned required.

We interrogated 450 patients (with coronary disease, ACS presence, ambulance apell, transfer to a first hospital for initial treatment end the second transfer to the cardyologic center for FT or PCI) about the atitude in case of chest pain onset.

The answers were:

a) open the windows to recive more oxigen – 68%
b) took treatment – please say what: antalgic (Algocalmin or another) – 36%; aspirin – 23%; Nitroglycerin – 86%; β-Adrenoceptor blockers – 15%.
c) both variants (a. and b.) – 0%
d) you didn't took treatment without doctor indication – 23%
e) did you call the EMS – 94%
f) did you alarm your nigh bours or relatives – 50%
g) did you only lie down – 23%
h) did you wait quiet the pain to disappeared – 26%
i) did you call for your own family doctor: - 59%; successfully – 13%; unsuccessfully – 46%
j) did you call for your cardiologist 3%
k) did you took "OANA-β"treatment – 14%.

We can notice that only 14% of patients took the whole "OANA-β"treatment. Most of them took Nitroglycerin 86%, or more air (oxigen) 68%, or antalgic 36%. Remarcable is also

that only 23% took Aspirin and only 15% took β-bloker. During the specialised medical tranport, from all the patients who called the EMS, only one third (34%) recived the whole"OANA-β"treatment on the ambulance. And what's hapened whith onother patients? They recived only a part of "OANA-β" or only oxygen, or nothing. We considered very important to know which are the real time interval between the first symptom of ACS (chest pain, dispnoe, etc.) and the right final treatment: fibrinolytic therapy (FT) or PCI (means "total ischemic time"). We asked for that our subjects. We made first a "time dissection" of entire interval "symptom – final treatment" and asked the subjects about them. These intervals were: "symptom – first drog", "symptom – 112 appeal", "112 – 112 (length of alarm message)", "112 – EMS at patient home", "length of emergency doctor consult", "transfer time to the first hospital", "length of medical consult in ED", " transfer time from the first hospital to the specialised cardiovascular hospital for FT or PCI", "time for cardiological diagnostic" and "time from doubtless cardiological diagnostic – FT orPCI". On an average, the time interval "symptom – TF" was 2hours and 47 minutes, and the other one, "symptom – PCI" was 3 hours and 37 minutes. We can see that now, in our country, is not yet possible to use the "gold ours" for fibrinolytic therapy or PCI. After the recommendations from the „ACC/AHA" 2004, holded from the „On-TIME"study, we can obtain the greatest patient's benefits if the total ischemic time is shorter then 2 ours. If we shell eliminate the "length of medical consult in ED", " transfer time from the first hospital to the specialised cardiovascular hospital for FT or PCI", "time for cardiological diagnostic", we'll make a time economy over one our (65 minutes in our study). That means that, even in our country, if we'll make the right cardiological diagnostic at patient's home or in ambulance, we'll avoid a very important time waste. We have interrogated about the same problems 200 practitioners (20 cardiologists, 80 emergency medicine specialists, 40 working in Ambulance services and 40 in emergency departament and, 100 family doctors). 86% of them consider that in our country, today is not real to speak about "gold hours" utilizations or fructification. From the other 14%, which are optimistic for "gold hours"fructification, 89% consider that we have to modify the prehospital emergency medical assistance and less the inhospital activity (11%).

About the causes of this deficient management of the medical assistance for ACS patients, the practitioners identified the following:

- patients are not educated for time economy – 86%
- known patients with coronary disease, are not instructed about the immediate attitude and treatment at the ACS symptoms onset – 82%
- family doctors don't act in the schorter time – 98%
- family doctors are not called, implicated and states rewarded – 96%
- family doctors don't know very well the new guidelines for ACS immediate attitude and treatment – 78% (By a direct interrogation, one of three questioned practitioners recognized that he doesn't know the new guidelines for ACS!!!)
- ambulance services don't react promptly – 76%
- ambulance services are not enough endowed – 100%
- the emergency care providers don't know the guidelines for ACS – 78%
- doesn't exists enough fibrinolytic drogs – 100%
- specialized centers for FT or PCI are too rarely and work only 8H daily – 100%.

The percentage is speaking him for each cause. Questioned practitioners considered also, that the patients triage must be doing in the prehospital area (63% of them), but they recognized too that the

family doctors and emergency doctors are not yet ready to make a doubtless cardiological diagnostic. The practitioners identified some causes which oppose to prehospital triage of ACS patients:

- it is not any interest for this problem in the health administration – 94%
- practitioners from the prehospital care in ACS, are not enough instructed for that – 78%
- practitioners from the prehospital care are not able to assume themselves the triage responsibility – 82%
- the prehospital area are not enough edowed with material and human resources – 100%
- the idea has not financial support – 100%."

We think that these are the most significant answers and, the percentage is speaking himself too, for each cause.

CONCLUSION:

In our country is not yet possible to make the ACS patients triage in the prehospital emergency medical assistance. We have to tray to change the entire system of emergency medical assistence, in prehospital and hospital sectors, in the sense of time economy. That means changes in human resouces instruction and changes in material resources too (endowment). The family doctors are not enought implicated in emergency medical assistance of ACS. In the prehospital area are not an adequate colaboration between the diferent medical servicies: patient, family doctors, 112-service, ambulance servicies, emergency departaments, specialised cardiovascular centers. The coronarian patients are not enough educated for theyrself helth, for the first atitude and treatment immediatly after the chest pain onset. The prehospital triage can be the best solution to avoid the time waste.

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PAGES 37-42

EVALUATION OF NASAL OBSTRUCTION WITH RHINOMANOMETRY AFTER NASAL PROVOCATION IN ALLERGIC RHINITIS

TOMA ANA-OLIVIA[1], FARA L.[1], POENARU MĂRIOARA[2], BUNU CARMEN[1], SARĂU C.[1], HORHAT DELIA[1], HORHAT RALUCA[2], STĂNESE ANA MARIA[2], MOCANU VALERIA[1]

[1] University of Medicine and Pharmacy "Victor Babeş" Timişoara
[2] ORL Clinic Timişoara

Correspondence to:
Ana-Olivia Toma, MD, University of Medicine and Pharmacy "Victor Babes" Timisoara, Spl.T. Vladimirescu no.14A, phone number: 0741 479926, email: oliviatoma@gmail.com

ABSTRACT

***Backround**: Allergic rhinitis is a frequent disease and the nasal obstruction is one of the major symptoms of allergy rhinitis and commonly requires medical treatment. Rhinomanometry is a method for measuring the severity of nasal obstruction. It is the synchronous measurement of the nasal flow and the difference in pressure between the choana and anterior nostril.*

***Objective**: The nasal provocation test was applied to all the patients in the study group, followed by rhinomanometry. We followed the symptoms according the symptom score and we compared the correlations with the rhinomanometry.*

Material and methods: 20 subjects (10 women and 10 men) aged between 18 and 47 years participated in the study. The series was collected from pacients enrolled in a follow-up study of allergic rhinitis. All the patients were diagnosed with perennial allergic rhinitis between 2009- 2010. Exclusion criteria were pregnancy, allergic asthma, considerable septal deviation, serious internal or neurological diseases, age younger than 18 or over 65 year, and pacients under continuous medication like steroids, where pharmacotherapy could not be stopped in time.

***Results**: The symptoms at presentations were: nasal obstruction in all the 20 patients (100%), serous rhinoreea in 18 patients (90%), sneezing in 12 patients (60%), itching in 10 patients (50%) and extranasal symptoms like lacryorhea, itching of the palate, itching of the ears, conjuntivitis, chemosis, urticaria, coughing in 12 patients (60%). We have observed semnifical correlation between the prick test and the variation of the flow in AAR (r =0.5).**Conclusion**: Only if there is a satisfactory correlation between rhinomanometry results and subjective sensation of nasal airflow, can rhinomanometry serve as a relevant criterion for evaluation of the result of nasal surgery or provocation or for determining indication for surgery. Our results indicate that rhinomanometry does reflect nasal obstruction, although there are some possibilities of error. Until other methods have been proved better, rhinomanometry can be used as a fairly reliable tool in assessing nasal patency.*

Key words: Allergic rhinitis, rhinomanometry, nasal obstruction.

INTRODUCTION

Nasal obstruction is one of the major symptoms of allergy rhinitis and commonly requires medical treatment. How ever an objectiv method is needed to

assess symptoms when evaluating the efficacy of medication. The subjective rating of symptoms remains the principal method for measuring the severity of nasal obstruction. In some disorders, such as ozaena or septal deformity, subjective asssesment of obstruction has sometimes been found to be surprisingly unreliable, but usually we assume that if the nose is blocked, it will feel blocked.For measurement we used an active anterior rhinomanometer. Rhinomanometry is the synchronous measurement of nasal flow and the difference in pressure between the choana and anterior nostril. The active anterior rhinomanometry is considered to be the most common physiologic method. With this method the flow is measured at the closed side of the nose. One side of the patient's nose is closed by a soft adapter made of foammaterial. For measuring the choanal pressure a tube is connected to the adapter. The patient's nose can either be closed by a plaster or an adapter. The measurement of the flow at the free side of the patient's nose is performed via a tightly sealing face mask. A few breath (5 breath are recommended) are sufficient to measure and evaluate flow and nasal airway resistance. Then the other side of the nose is closed and the free side is measured. The parameters and the resistance curve of each test are calculated and displayed on the screen. The assesment of the measured values as well as the analysis of the resistance curves provide information about the permeability, i.e. the resistance behaviour of the nose.

MATERIAL AND METHODS:

20 subjects (10 women and 10 men) aged between 18 and 47 years participated in the study. The series was collected from pacients enrolled in a follow-up study of allergic rhinitis. All subjects had symptoms when initially studied. Subjects who presented with upper respiratory tract infection or who were unable to grasp the concept of the visual analogue scale were not accepted for the study of nasal obstruction assessment.

All study participants underwent an otorhinolaringology examination including anterior rhinoscopy and endoscopy of the nasal cavity. They had no history or sinonasal surgery. Exclusion criteria were pregnancy, allergic asthma, considerable septal deviation, serious internal or neurological diseases, age younger than 18 or over 65 year, and pacients under continuous medication like steroids, where pharmacotherapy could not be stopped in time. Antiallergic treatment (oral or nasal antihistamines, cromolyn sodium and nasal decongestionant) had to be stopped least 5 days prior to study participation. The skin prick test was negative for all of the pacients. Specific IgE of Dermatophagoides pteronyssinus and Dermatophagoides farinae and the other skin tested allergens was determinated. Nasal provocation test: The provocation tests with allergens are important methods of examination which give information about pathophysiology and immunological mechanism of allergic diseases of the upper respiratory tract. They are firmly established in diagnosing such diseases. If the disease becomes manifest at both, the upper and the lower respiratory tract, positive nasal provocation tests, instead of bronchical provocation tests, will be considered to be a proofof a relevant sensitization. Negativ results of a nasal provocation test, however, cannot be used for an assessment of the lower respiratory tract. Not more than 2 allergenic extracts are to be tested per day.

Indications:

- ensuring the diagnostis if anamnesis and antigen provocation test do not correspond;
- proof of sensitizatoin to allergens which is not discernible from anamnesis;
- reproduction of a clinical picture without considering pathogenesis if an antibody cannot be detected but anamnesis ahows than an

inhalationally produced disease is suspected.

Contraindications:
- acute, inflamatory disease of the nose or the paranasal sinus;
- if other manifestation organs show an acute allergic raction of early reaction type;
- not standardized allergenic extracts and native allergens are used whose adequate dosage is not known;
- in case of pregnancy.

Accompanying therapy in nasal provocation tests:

Table 1 wating period according to the allergic therapy administrated

Drug	Waiting period
DNCG, nasal	3 days
Adrenocortical steroids, nasal	14 days
Inhaled bronchospasmolytics	None
Adrenocortical steriods(oral)	7 days
H-blockers	1-42 days
Non-steriod analgetics	7 days
Centrally effective antihypertesives	21 days
Tricyclic psychopharmaceuticals	21 days

The test protocol is presented in 2. Before the first acoustic rhinometry and rhinomanometry (at −30 min) the subjects were acclimatized for at least 30 min. We used a dilution (1:10) of the allergen extract. Two puffs of the diluent solution from a nasal pump spray was delivered into both cavities at the time point −30 min and then two puffs of the antigen solution on one side and the diluent solution correspondingly on the other side at the time point 0 according to the protocol. The allergen solution was applied into the more patent cavity (according to rhinomanometry) at the time point 0. The allergen solution and the control solution contralaterally were delivered at 15 min intervals unless an obvious clinical response occurred (several sneezes, abundant secretions from the nose and eyes). The nasal secretions were always aspirated before the rhinomanometry.

Table 2 The nasal provocation test protocol (NS- aspiration of nasal secretion, AAR- active anterior rhinomanometry)

Time point	*Antigen cavity*	*Control cavity*
-30 min	NS, AAR, diluent spray	NS, AAR, diluent spray
-15 min	NS, AAR	NS, AAR
0 min	NS, AAR, antigen sray The more patent cavity in AAR	NS, AAR, diluent sray The less patent cavity in AAR
15 min	NS, AAR, antigen spray unless obvious clinical reaction	NS, AAR, diluent spray if antigen delivered on the other side
30 min	As before	As before
45 min	As before	As before
60 min	NS, AAR	NS, AAR

Assessment of reaction: The nasal mucous membrane basically shows three symptoms when reacting to stimulations kind. These are: obstruction, secretion, irritation.

Provocation tests with allergens can cause distance symptoms such as conjunctival reaction, itchting in the ears as well as coughing or dyspneea. These symptoms as well as secretion and irritation should be evaluated in a symptom score.

The reaction is evaluated to be positive if a symptom score of more than 3 points is achieved.

Nasal obstruction is assessed with help of a suitable method for measuring the nasal flow resistance.

A positive result of the provocation test is indicated by an increased nasal flow resistance or a reduced volum flow. Secretion is assessed by a semi-quantitative assessment of the amount of secretion.

- no secretion 0 point
- little sectretion 1 point
- much secretion 2 poits

Irritation: is estimated by counting the sneezing attacks:

- 0-2 sneezing 0 point
- 3-5 sneezing 1 point
- 5 snnezing 2 point

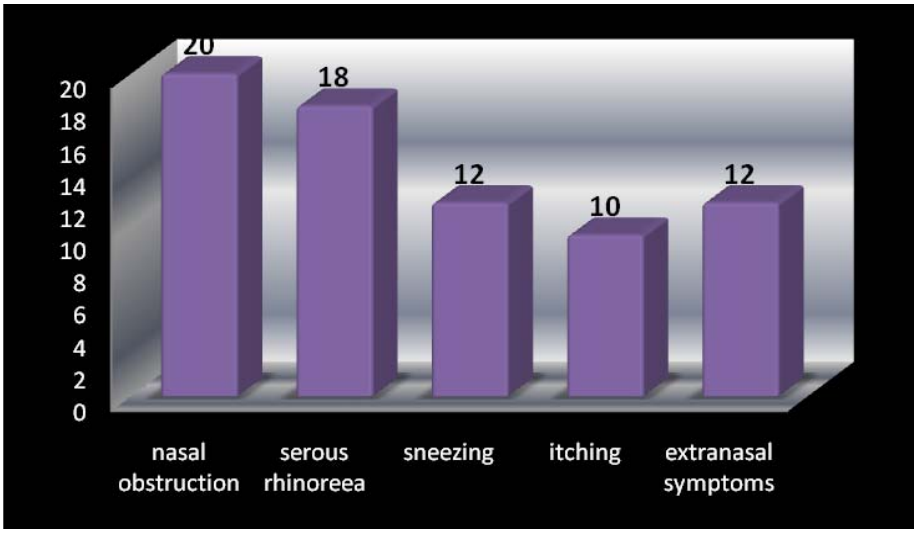
Distant simptoms:

- 1 point lacryorhea and/or itching of the palate and/or itching of the ears
- 2 points conjuntivitis and/or chemosis and/or urticaria and/or coughing and/or dyspnea.

RESULTS:

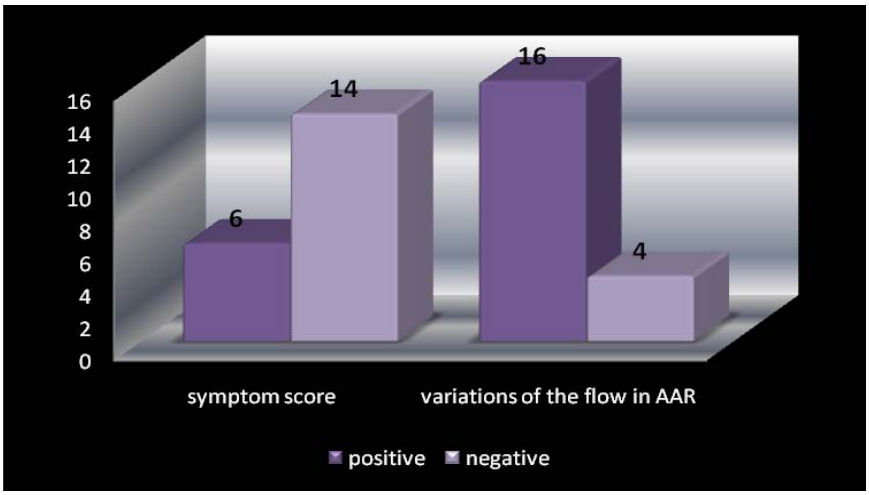
The study group consisted of 20 patients (50% males, 50% females). The median age was 28.8±9.28 years. All the patients were diagnosed with perennial allergic rhinitis between 2009- 2010.

The symptoms at presentations were: nasal obstruction in all the 20 patients (100%), serous rhinoreea in 18 patients (90%), sneezing in 12 patients (60%), itching in 10 patients (50%) and extranasal symptoms like lacryorhea, itching of the palate, itching of the ears, conjuntivitis, chemosis, urticaria, coughing in 12 patients (60%).



Allergy has been demonstrated with the „prick test", which was positive at all the 20 patients (100%). The allergens the most frequently incriminated were: dust, molds, pollens and mites.

Rhinomanometry was performed to all the patients of the study group. 16 patients (80%) presented variations of the flow in AAR. The symptom score was positive after provocation at 6 patients (60%).



DISCUSSIONS:

Allergic rhinitis is a frequent disease, approximately 40% of the population present nasal symptoms during their lifetime with geographical variations. It is not a severe disease, but it can influence unfavorably the social activity and can associate with asthma, sinusitis, otitis media, nasal polyposis, infections of the upper airways. We have observed a significant correlation between the prick test and the variation of the flow in AAR(r =0.5). Long-term adaptation to nasal obstruction could be expected to lead to poor correlation between subjective and objective parameters, but among our patients this phenomenon could not be seen. However, the variation in subjective scoring suggests that every nose is individually calibrated. In principle, it should be easy to calculate nasal airway resistance by measuring the pressure gradient and air flow through the nasal cavities. In practice, several factors can affect the results and make assessment more complicated. Change in mucosal swelling, the position of the soft palate and the form of nostril may have influenced rhinomanometry results which seem inconsistent with subjective assessment. Technical difficulties, e.g. leakage and occlusion, can lead to similar discrepancies. Reproducibility can be poor, which decreases the value of the method. In a study by several investigators, differences in performing rhinomanometry may also produce variation. In our study, all measurements were carried out by one person according to a strict protocol with special emphasis on minimizing technical errors. Some earlier studies have suggested a discrepancy between objective and subjective assessment in normal subjects. The sensation of the symptomless nose may correspond with a rather wide range of nasal resistance values, which may be one reason for the discrepancy. In the present study, most of the measurements were made in noses with pathological resistance. In practice, rhinomamometry provides the most useful information in patients with nasal symptoms, whereas measurements in asymptomatic subjects are of limited value. Only if there is a satisfactory correlation between rhinomanometry results and subjective sensation of nasal airflow, can rhinomanometry serve as a relevant criterion for evaluation of the result of nasal surgery or provocation or for determining indication for surgery. Our

results indicate that rhinomanometry does reflect nasal obstruction, although there are some possibilities of error. Until other methods have been proved better, rhinomanometry can be used as a fairly reliable tool in assessing nasal patency.

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PAGES 43-45

CARIES INFILTRATION- ICON

SARMAS EVANGHELOS[1], GUJBĂ (ROŞU) ANITA[2], POPOVICI-MUŢ ANA-MARIA[3], ELENI THEODORIDOU[1], PODARIU ANGELA[2]

[1] Private Practise, Greece
[2] Department of Preventive Dentistry- Victor Babes University of Medicine and Pharmacy, Timisoara, Romania
[3] Faculty of Medicine and Pharmacy, University of Oradea, Romania

Correspondence to:
sarmas.evanghelos@gmail.com

ABSTRACT

Utilising the latest scientific advances in materials and techniques, Minimally Invasive Dentistry allows dentists to perform advanced techniques. Until now, dental professionals have had only two choices in the treatment of caries: use fluoride and other treatments to remineralize enamel in the very early stages – or "wait and see" until it's time to "drill and fill." Developed to treat incipient caries, Icon is a caries infiltrant that incorporates micro-invasive technology to fill, reinforce, and stabilize demineralized enamel without drilling or sacrificing healthy tooth structure.

Key words: Icon, white spot, cavity, prophylaxis.

INTRODUCTION

DMG America, a dental technology company out of Englewood, N.J., is selling a light cured infiltrant resin that is useful for treating early cavities. At the very early stage of tooth decay, before a formal, treatable cavity has developed, fluoride treatment is often used as prophylaxis. But after a certain level of tooth decay, fluoride will be of no use, yet drilling the tooth to treat the cavity is not merited either, since filling a cavity with this method destroys healthy tooth tissue, and it is uncertain whether the decay will continue to a point that requires treatment. Dentists at this stage usually wait to see how the tooth decay progresses, but the Icon system gives dentists another option and allows them either the ability to treat decay that they view as particularly vulnerable to progression or treat a patient who they view as not likely to practice healthy dental hygiene. The technology is also useful for the treatment of cariogenic white spot lesions.Icon can be used to treat smooth surface and proximal carious lesions up to the first third of dentin (D-1). In a single patient visit, Icon can arrest the progression of early enamel lesions and remove white spot lesions.

Incipient Caries

Incipient caries is characterized by demineralisation under a seemingly healthy surface layer. In the lesion body of incipient caries, the pore volume resulting from mineral loss can be more than 30%.

This manifests itself in the form of white opaque spots, so called "white spots". The pores in the lesion body of incipient caries create diffusion paths for the cariogenic acids. In addition minerals dissolved from the enamel are also lost in this manner, leading to a further demineralization of the lesion body through the pores.

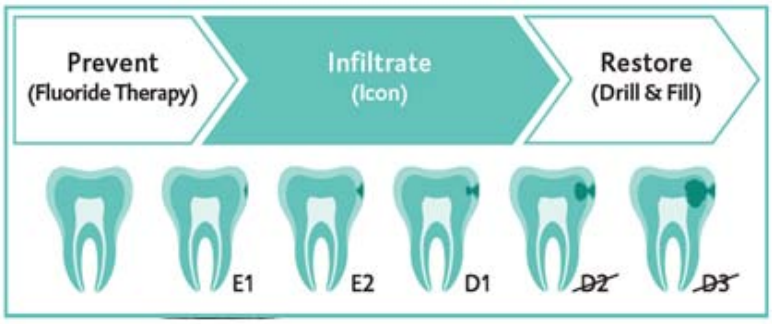

Fig.1 The first treatment to bridge the gap between prevention and restoration

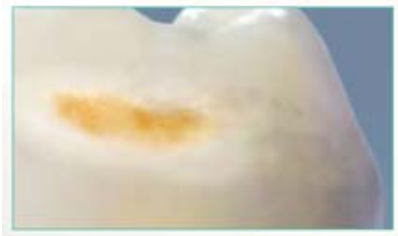

Fig.2 Clinical image of an incipient caries lesion

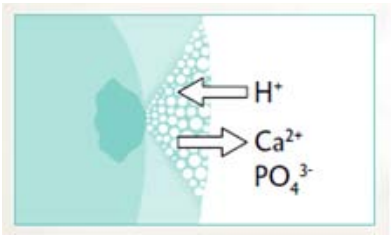

Fig.3 Pore system of an incipient caries

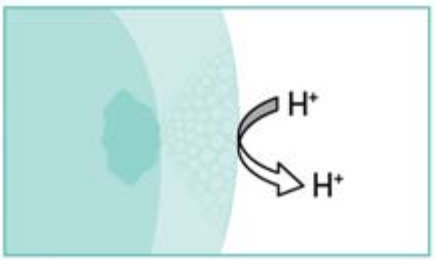

Fig.4 Icon blocks the diffusion paths

Fig.5 Icon Kit

Fig.6 Lesion before Icon treatment

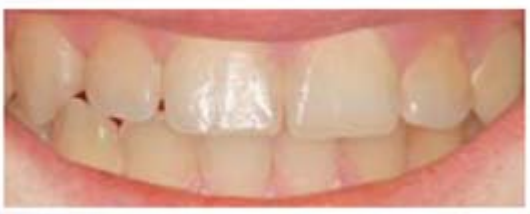

Fig.7 After Icon treatment

Icon offers a simple alternative to the "wait and see" approach, enabling immediate treatment without unnecessary loss of healthy tooth structure. Icon prevents lesion progression and increases life expectancy for the tooth. Icon also provides a highly esthetic alternative to microabrasion and other restorative treatments for cariogenic white spot lesions; white spot lesions infiltrated by Icon take on the appearance of the surrounding healthy enamel.

Use of Icon is described as simple and user-friendly: After isolating the tooth with rubber dam and placing wedges to separate the teeth, the tooth surface is prepared with a 15% HCL gel to open the pore system of the lesion body. Next, the surface is rinsed, dried with ethanol, and further dried with air. The Icon Infiltrant resin, which has a high penetration coefficient, is applied onto the lesion, excess material is removed, and the material is light cured. The manufacturer recommends applying a second layer of the infiltrant, followed by additional light curing.

CONCLUSION

- Painless method without anesthesia or drilling;
- A Definitive Treatment;
- Preserves healthy tooth structure;
- Increased life expectancy of the tooth;
- Treatment in one sitting;
- Early treatment of at risk patients with poor compliance.

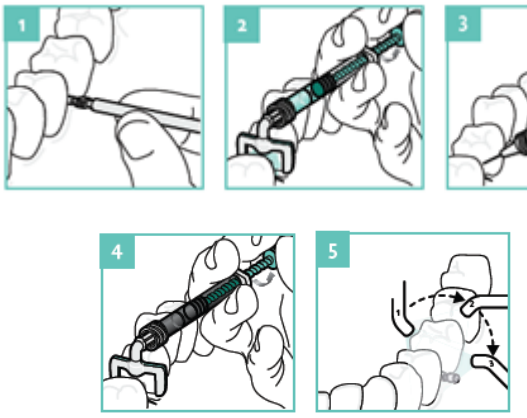

Fig.8 Proximal procedure

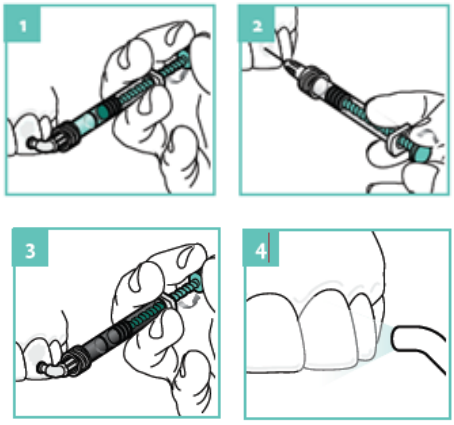

Fig.9 Smooth surface procedure

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THE RELEVANCE OF PROGNOSIS FACTORS IN THE THERAPEUTIC DECISION MAKING AND EVOLUTION OF PATIENTS SUFFERING FROM AGGRESSIVE NON-HODGKIN LYMPHOMA

DACIAN OROŞ[1], IOANA IONIȚĂ[1], MIHAI IONIȚĂ[2], HORTENSIA IONIȚĂ[1]

[1] Department of Hematology, University of Medicine and Pharmacy "Victor Babeş" Timişoara
[2] Department of Medical Semiology, University of Medicine and Pharmacy "Victor Babeş" Timişoara

Correspondence to:
Dacian Oros, MD, PhD, Department of Hematology, University of Medicine and Pharmacy "Victor Babes" Timisoara, E-mail: dacianoros@gmail.com

ABSTRACT

Without any doubt the nowadays known clinical and paraclinical elements as well as the prognosis factors only represent the expression of heterogeneity and biological complexity of Non Hodgkin Lymphoma (NHL), but it is also obvious that the ensemble of infrastructural and molecular parameters affect the evolution and prognosis of NHL patients in the most profound way 9.

Material and methods: The present study refers to the recognition and correlation of prognosis factors with the treatment and evolution of patients and was undertaken on a group of patients, the essential selection criteria being the framing in the agressive (medium and highly agressive) non-Hodgkin lymphoma category as seen from the clinical, hystological and immunological point of view. 134 patients have been studied during 2006-2008. The prognosis factors that have been studied are: factors that depend on the individual, factors that depend on the tumor mass and biological factors. The data obtained in this study has been structured as follows. The considered prognosis factors have been divided into three categories: general, clinical and paraclinical.

Conclusions: Male gender has been more frequently associated to an advanced clinical stage. The existence of B signs in elderly patients represents a negative prognosis factor. The best results have been obtained in young patients, phenotype B, without other associated conditions, in early stages, without B symptoms, without extra-nodal or marrow determination.

Key words: agressive Non Hodgkin Lymphoma, prognosis factors, evolution, treatment

INTRODUCTION

The complexity of lymphoma cytogenesis is given by numerous stages of lymphocyte differentiation, that doesn't resume to the simple division of B and T lymphocytes [1, 2]. Non Hodgkin lymphoma (NHL) do not represent a disease but are a heterogeneous group of clinical-biological entities that have as a starting point malignant transformation of B,T,NK (natural killer) lymphocytes and histiocytes. This translates into a morphological, biological and clinical diversity of NHL[3].

Objectives: Worldwide, multiple studies have been preocupied to establish prognostic models that correlate clinical-biological pretherapeutic variables with survival and evolutional profile [1]. Using series of patients, through multivariate statistical studies, a series of predictive variables have been detected and used to establish prediction models for the death risk [7, 8].

Without any doubt the nowadays known clinical and paraclinical elements as well as the prognosis factors only represent the expression of heterogeneity and biological complexity of NHL, but it is also obvious that the ensemble of infrastructural and molecular parameters affect the evolution and prognosis of NHL patients in the most profound way [9].

Aiming to create a prognosis model that is easy to design, reproducible and based on clinical-biological simple criteria, we tried to correlate prognosis factors with the evolution and treatment of patients [10, 1]. This paper wants to clarify, identify and contour prognosis factors, but also to demonstrate their interdependency regarding specific clinical aspects as well as treatment and evolution of patients suffering from aggressive non Hodgkin lymphoma. The difficulty and controversy in establishing prognosis factors resides in the fact that there isn't any clear and efficient method to classify NHL, because of the diversity and multitude of characters. During the last decades, the introduction of targeted molecular therapies but also modern techniques of chemotherapy have revolutionized the treatment of these conditions, attracting the necessity to define prognosis factors which influence the treatment response [4, 5].

MATERIAL AND METHODS

The present study refers to the recognition and correlation of prognosis factors with the treatment and evolution of patients and was undertaken on a group of patients diagnosed and treated at the Haematology Clinic part of the Emergency Municipal Clinic Hospital Timisoara, the essential selection criteria being framing them in the agressive (medium and highly agressive) non-Hodgkin lymphoma category as seen from the clinical, hystological and immunological point of view. 134 patients have been studied during 2006-2008. The prognosis factors that have been studied are: factors that depend on the individual: age, gender, living conditions (rural-urban areas); factors that depend on the tumor mass: presence of tumor masses (bulky disease: mediastinal adenopathy >1/3 of the toracal diameter, peripheric adenopathy and/or abdominal having the maximum diameter over 5 cm), presence of extranodal determination, presence of hepathomegalia and splenomegalia. Biological factors: ESR > 30 mm/h with the presence of „B" signs of disease and ESR>50 mm/h in the absence of signs, LDH isoenzyme value, value of reactive protein C, presence of immune alterations, initial haemoglobin value < 10 g/dl, value of seric albumin, level of beta-2 microglobulin, presence of marrow involvment (concordance with the hystological type of the lymphoma), hystologic type, cell phenotype, immunohystochemical markers having prognosis value: CD20, CD44, BCL-212, Ki-67, presence of cytogenetic anomalies [8], association of viral infections that have been serologic documented: HIV, HCV, HBV, EBV, HTLV-1.

The analysis of the mentioned biologic parameters has been done using specific methods by the laboratories at the Haemathology Clinic Timisoara, Municipal Hospital, the genetic and molecular biology laboratories at the UMPh „Victor Babes" and the Bioclinica laboratories.

The therapeutic protocol has been guided by the modern international treatment principles, has been individualized and based mainly on polichemotherapy – first generation (CHOP,CVP), second generation (ProMACE, M-BACOD, COP-BLAM, CAR-BOP) and third (ProMACE-CytaBOM, MACOP-B, VACOP-B), associated with radiotherapy, monoclonal antibodies (Mabthera), interferon, surgical removal of

the tumor according to the clinical, paraclinical and immunohystochemical picture [5, 6, 11]. The data obtained in this study has been structured as follows. The considered prognosis factors have been divided into three categories: general (age, gender), clinical (symptoms, stage) and paraclinical (LDH, ESR, leucocytes, lymphocytes). The gender division was relatively equal (69 men, 65 women) – table 1, the average age at the beginning being 60 years, 31% showed accelerated ESR (>30 mm/h) associated with B signs, 12% had ESR>50 mm/h in the absence of B signs, 23% increased number of leucocytes, 26% decreased number of lymphocytes. 38% presented high LDH levels in their diagnosis. Most of the patients were diagnosed in an advanced stage of disease (III-37% or IV-33%) – table 2, associated with B signs (57%) and high LDH; Lymph nodes determination (66%) and extra lymph nodes determination 34% - table 3 and marrow affectation 14%. The LDH level pre-treatment showed relevant values to the clinical stage, with sensitive higher level for the advanced stages (III and IV), as compared to the early stages (I and II) but high LDH levels in early stages were correlated with the tendency to early relapse post-radiotherapy.

Table 1

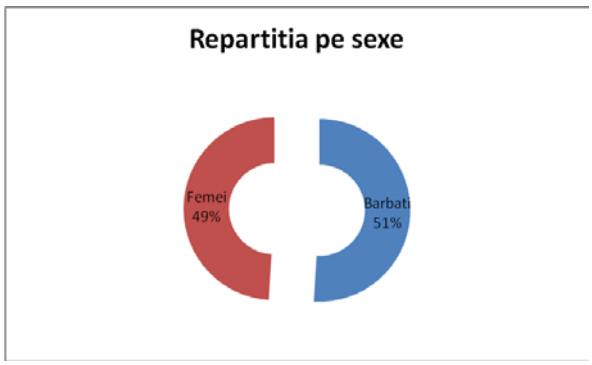


Table 2

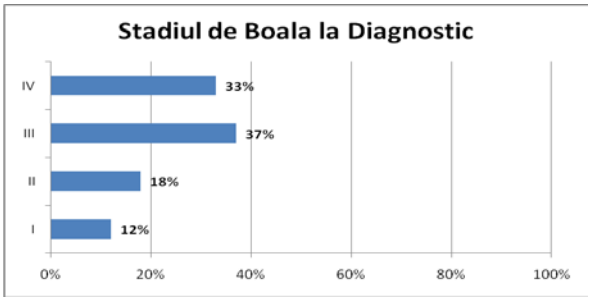
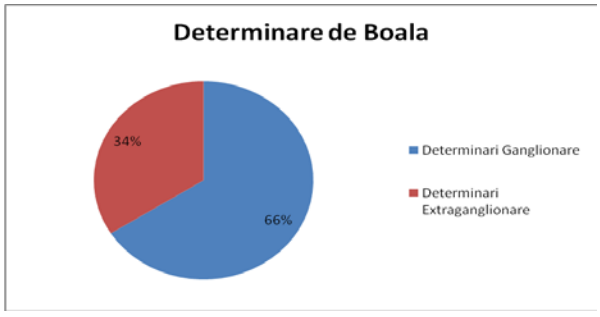
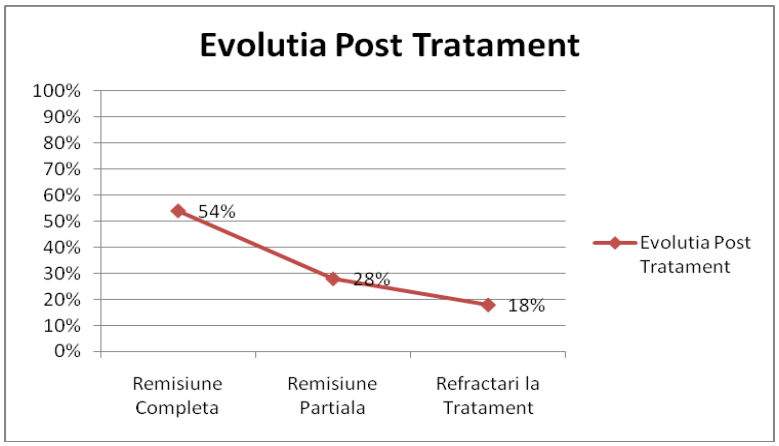


Table 3



Complete remission was obtained in 54% of the patients, partial remission in 28% and 18% were reluctant to treatment – table 4.

Table 4



CONCLUSIONS

Male gender has been more frequently associated to an advanced clinical stage, with B signs and a more agressive hystology. The existence of B signs in elderly patients represents a negative prognosis factor, along with agressive hystology and high LDH levels. Modest results have been obtained in elderly patients, because of the low rate of complete remission and early relaps. High levels of ESR have been associated to a low level of complete remission.

High LDH levels indicate a more immature tumor phenotype with the tendency to agressive evolution and resistance to treatment. It has been observed that a high LDH level at the beginning was associated to a lower rate of complete and partial remission. The LDH level is correlated to the extranodal disease determination, representing an unfavorable prognosis factor. The best results have been obtained in young patients, phenotype B, without other associated conditions, in early stages, without B symptoms, without extra-nodal or marrow determination.

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EFFECT OF EXTERNAL TOOTH BLEACHING ON DENTAL PLAQUE ACCUMULATION

IMOLA BUKA[1], CSILLA BENEDEK[1], MIHAI POP[1] , GHEORGHE MATEKOVITS[2]

[1] UMF Tg.Mureş, Faculty of Dental Medicine, Discipline of Odontology-Periodontology
[2] UMF Victor Babeş-Timişoara, Faculty of Dental Medicine, Discipline of Oral Rehabilitation, Dental Tehnition Speciality

Correspondence to:
Dr. Buka Imola buka_imola@yahoo.com, tel: 0749072794

ABSTRACT

Treatment of dental discoloration with external bleaching is becoming very common in dentistry; however, possible irreversible alterations on enamel surface due to bleaching procedures make up for a topic of controversy in the literature. The aim of this study was to evaluate the clinical effects of bleaching by measuring the dental plaque accumulation on human enamel, in vivo.

Methods: Eighteen volunteers (12 women, 6 men) with dental discoloration, but not revealing any restorations or periodontal problems were assigned for this study. Bleaching agent gel with 35% hydrogen peroxide was applied only to labial surfaces of upper arch teeth. After a classic clinical examination dental plaque accumulation was measured with two plaque indexes after a non-brushing period of 30 hours pre- and post-bleaching.

Results: The results of the comparison of pre- and post-bleaching measurements showed, that after the non-brushing period plaque accumulation scores for bleached surfaces were lower than the non-bleached surfaces scores.

Conclusions: According to the results obtained in this short term in vivo study, ex-ternal vital bleaching with 35% hydrogen peroxide seems to discourage plaque accumulation on bleached human enamel after a non-brushing period lasting more than a day.

Key words: treatment bleaching, plaque accumulation, 35% hydrogen peroxide, tooth discoloration

INTRODUCTION

Tooth discoloration is a frequent reason for patients to address cosmetic treatments. Nowadays a growing number of patients demand for whiter teeth through bleaching (1). Generally tooth discoloration can be classified as extrinsic (localized on the exterior surface of the tooth), intrinsic (localized inside the tooth structure) (2, 3) or combination of both (4). Scaling and polishing of teeth are conventional treatment choices for extrinsic tooth discoloration, however for stubborn discolorations and intrinsic stains, bleaching techniques may be needed (5). Present tooth bleaching techniques commonly use hydrogen peroxide as active agent. Hydrogen peroxide may be applied directly, or produced in a chemical reaction from sodium perborate or carbamide peroxide (6, 7). Concentration of hydrogen peroxide seems to affect the success of bleaching procedure, together with the

duration and the num-ber of times the agent is applied (8, 9, 10). The majority of studies have usually analyzed the morphological changes on enamel surfaces after bleaching by different techniques. While in many researchers' opinion bleach-ing increases enamel surface roughness, our hypothesis is that this could favor an increase in plaque accumulation. The aim of this preliminary study was to evaluate short-term clinical effects of bleaching with 35% hydrogen peroxide. We examined the vestibular enamel surfaces of a group of patients before and after bleaching, in order to evaluate the differences in dental plaque accumulation on human enamel in vivo (11).

MATERIAL AND METHODS

The study sample (18 patients) is representative for target population and involves 18 patients; their gender distribution is 12 women and 6 men.

The patients enrolled in this study were volunteer healthy dental students from University of Medicine and Pharmacy from Târgu-Mureş and the research was accomplished during 2010. The inclusion criteria for subjects in examination group were:

- patients with dental discoloration, but without dental restorations and periodontal prob-lems;
- patients' cooperation: they followed the indications and restrictions before and after bleach-ing and were willing to come back for ulterior examination;
- the environmental origin of subjects: dental students from University of Medicine and Pharmacy from Târgu-Mureş, with ages between 21-24 years;

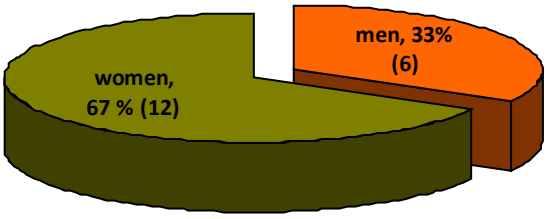

Chart 1.
Gender distribution of the examined group

Patients were asked to abstain from oral hygiene one day before bleaching, respec-tively to not brush their teeth at night and following morning, while the appointment took place in the afternoon. They could keep their alimentation habits, but chewing gum was ex-cluded. Practically they abstained from oral hygiene approximately 30 hours. Before bleach-ing, respecting the anterior indications the dental plaque was colored with 1% methyl blue, rinsing it properly a few minutes in the mouth. We took picture from initial status (Fig.3), than after a classical examination of the superior and inferior arch, using two different plaque index measurements simultaneously; results were noted in observation sheets. According to Turesky Modification of Quigley-Hein Plaque Index (11) (TPI), microbial den-tal plaque scored according to following criteria: 0- no plaque, 1- separate flecks of plaque at the cervical margin of the tooth, 2- thin continuous band of plaque up to 1 mm at the cervical margin of the tooth, 3- a band wider than 1 mm but covering less than 1/3 of the tooth, 4- plaque covering at least 1/3 but less than 2/3 of the crown, 5- plaque covering 2/3 or more of the crown (Fig.1). The plaque scoring in Rustogi Modification of Modified Navy Plaque Index (11)(MNI) is based on the presence or absence of plaque by a score 1or 0, on nine areas of tooth

surface. The sum of the scores is the MNI score of the tooth (Fig.2).

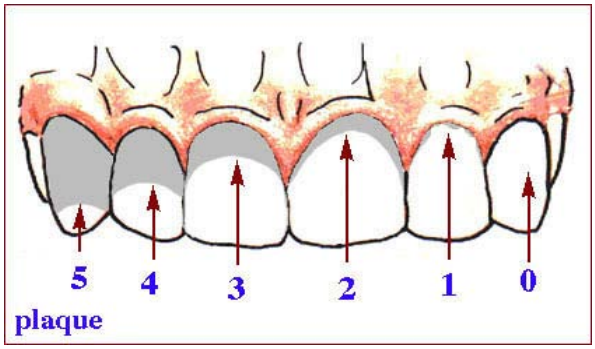

Fig 1.
Quigley Hein Index Modified by Turesky at al., 1970

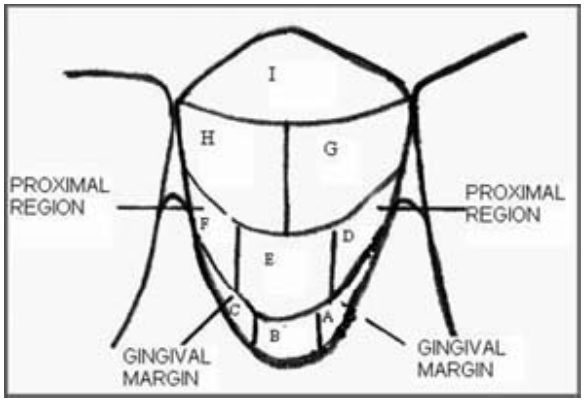

Fig 2. Rustogi Modification of Modified Navy Plaque Index (MNI).

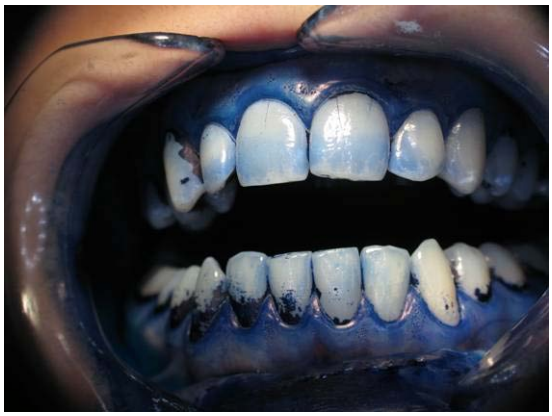

Fig.3. Colored dental plaque before bleaching.

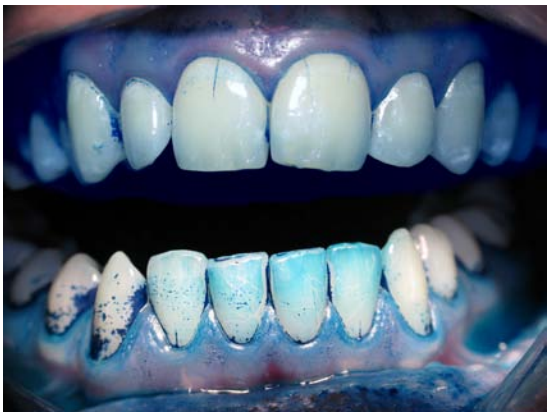

Fig.4. Coloured dental plaque after bleaching.

After determination of Plaque Indexes, protocol teeth were cleaned thoroughly with professional brushing from 1% blue methyl colored plaque. The initial color of superior arch participant teeth was determined with Classical Vita Shade Guide and a picture was taken (Fig.5). The inferior arch wasn't bleached and represented the control group. The bleaching procedure using 35% hydrogen peroxide primary active ingredient, followed the manufac-turer indications. Before using the bleaching gel a gingival barrier from a light curing material was

applied. The bleaching agent was applied in one session twice 8 minutes on the vestibular surfaces of superior arch teeth: 1.5-2.5 and removed with surgical suction and amply rinsed with water. The immediate color change was established with Classical Vita Shade Guide and a picture was taken (Fig.6). After two weeks using the same protocols and the patients followed the previous in-dications concerning the abstinence from oral hygiene one day before control, dental plaque was colored in the same way.

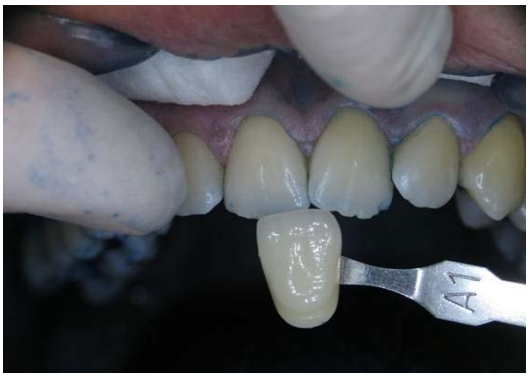

Fig.5. Colour determination before bleaching

Fig.6. Colour determination after bleaching

During a classical clinical examination plaque accumulation was determined with plaque indexes used initially and registered in the observation charts and pictures were taken (Fig.4). The bleached teeth were preventive scrubbed with fluoride solution, after a previous polishing, in order to stimulate remineralization and to prevent hypersensitivity, although just few of the participants complained of moderate hypersensitiv-ity for a few days. In order not to influence the study with modifying the plaque adhesion to bleached enamel surfaces, fluorization was accomplished just after the control period and not after the bleaching session. Results were statistically processed using descriptive statistics in Excel, Kolmogorov-Smirnoff in Graphpad normality test and Student t test.

RESULTS

Statistical analysis of Quigley- Hein Plaque Index (TPI) reveals:

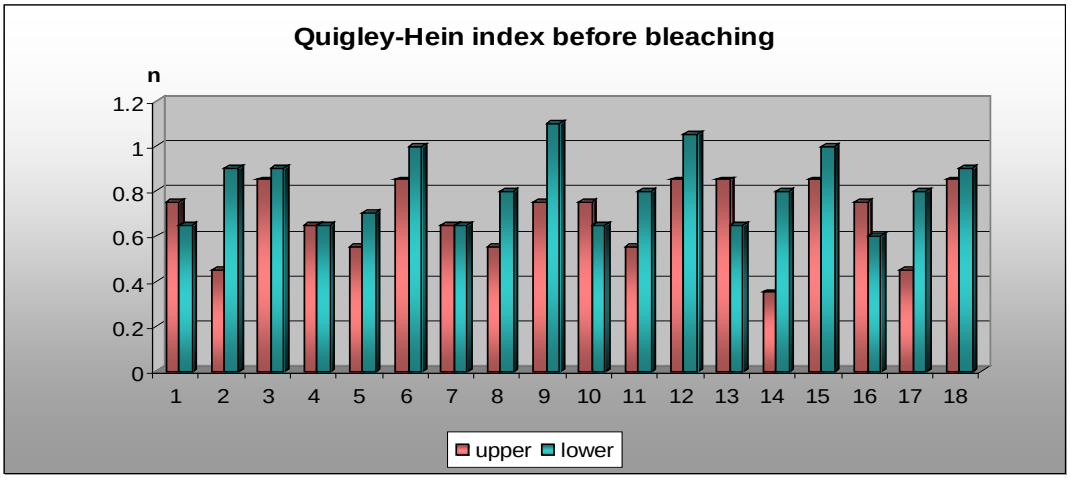

Chart 2. The values of Quigley-Hein Index before the bleaching of upper/ lower arch

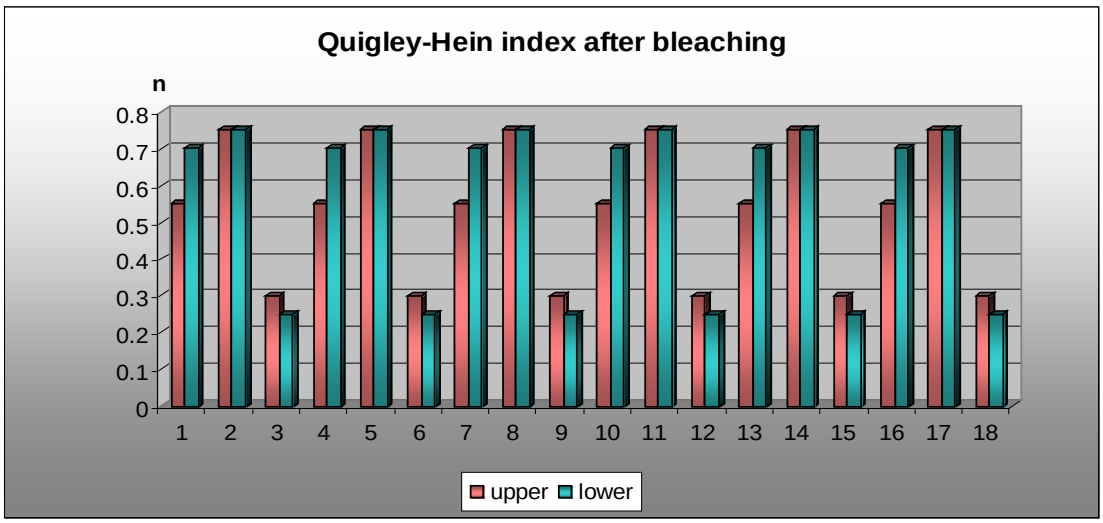

Chart 3. The values of Quigley-Hein Index after the bleaching of upper/ lower arch

Based on descriptive statistics, we can say that before bleaching the mean value of plaque accumulation of our group regarding to Turesky Modification of Quigley-Hein Plaque Index (TPI) was: 1.48, standard deviation: 0.25, sample variance: 0.07 and coefficient of variation (CV): 17.24. After bleaching a mean of 1.09 was found, standard deviation: 0.42, sample variance 0.18 and CV 38.92. The frequency distribution curve in both cases is flattened, before bleaching is asymmetric toward large values, and after bleaching to small values. Comparing the values of plaque accumulation on the arches we can say that there is an extremely significant difference ($p<0.0001$, CI = 95% = 0.08733-0.2127) regarding the average values of plaque accumulation on the maxillary dental arch before and after bleach-ing. In case of Rustogi Modification of Navy Plaque Index (MNI) we obtained the following results:

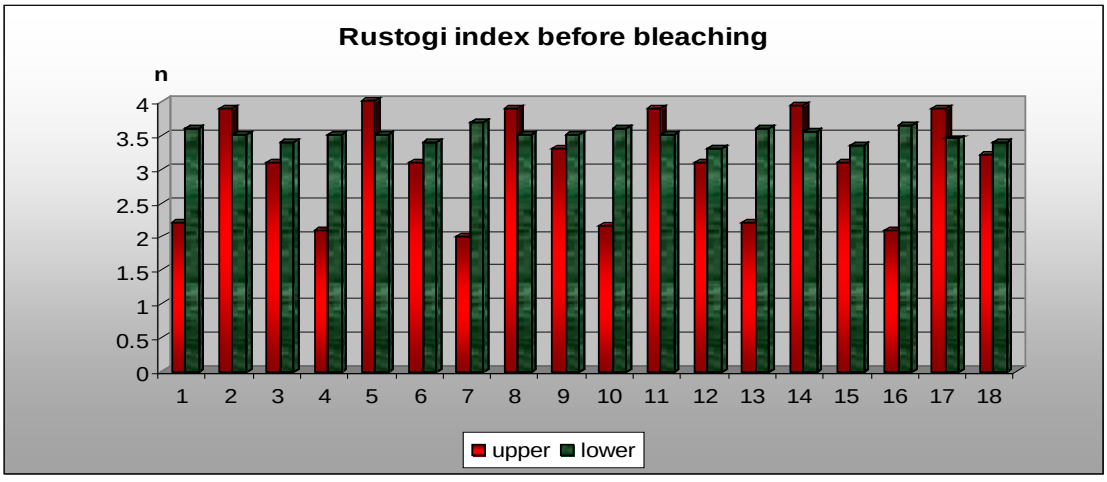

Chart 4. The values of Rustogi Index before the bleaching of upper/ lower arch

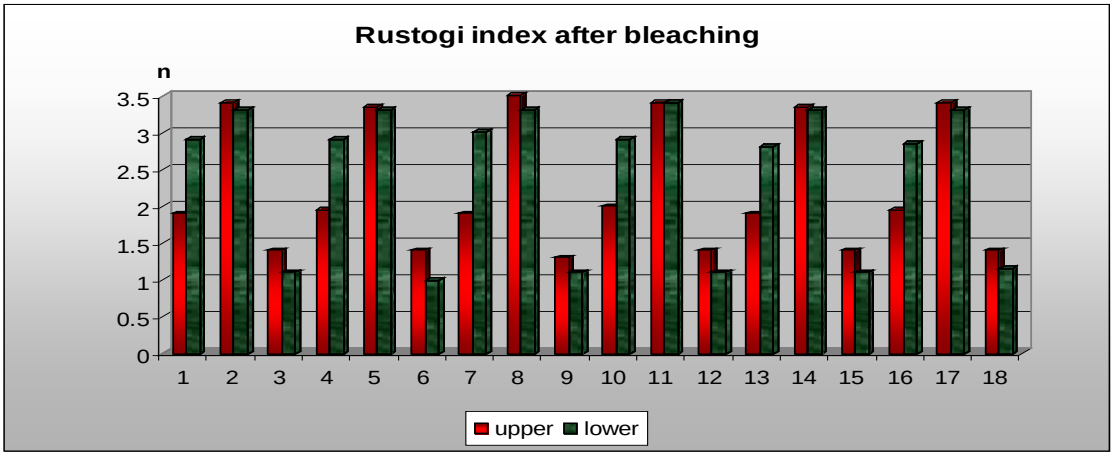

Chart 5. The values of Rustogi Index after the bleaching of upper/ lower arch

Using descriptive statistics we can say that before bleaching the mean value of our group plaque accumulation after Rustogi Index was: 3.31, standard deviation: 0.33, sample variance: 0.11 and coefficient of variation (CV): 10.07. After bleaching was found a mean of: 2.53, standard deviation: 0.75, sample variance: 0.57 and CV: 29.76. The frequency distribution curve in both cases is flattened, before bleaching is asymmetric towards large values, and after bleaching to small values. Comparing the values of plaque accumulation on the arches, taking in consideration the Rustogi Index, we can say that there is a very significant difference ($p<0.0001$, CI = 95% = 0.5170-1.150) regarding to the average value of plaque accumulation on the upper arch before and after bleaching.

DISCUSSION

The present study evaluated the effect of bleaching by 35% hydrogen peroxide on dental plaque accumulation in short term periods. According to the results presented statisti-cally and photometrically, after oral hygiene abstaining periods lasting 30 hours, respectively non- brushing periods of the teeth; the amount of dental plaque accumulation on bleached enamel surfaces were significantly lower than non-bleached counterparts. The role of dental plaque as an etiological agent of both dental caries and periodontal disease is indisputable. In healthy oral cavity, a dynamic equilibrium exists on teeth surfaces between forces of reten-tion and removal of dental plaque (18).

Rough surfaces promote dental plaque accumulation and maturation. There are con-troversies concerning the possible roughening effect of bleaching procedures on enamel sur-face. Some researchers sustain that after bleaching enamel surface roughness increases but others did not found significant morphologic differences between bleached and non-bleached enamel. Controversies in opinions and results may be explained with differences in study designs, use of different commercial bleaching agents with very va-rying pH 3.67-11.13 and because chemical composition and additive substances differ from one manufacturer to another.Morphological alterations of bleached human enamel have been usually analyzed with Scan-ning Electron Microscopy (SEM), Profilomether or Knoop Indentor in in vitro studies, although fewer or not significant alterations are expected in in vivo studies, due to the buffer capacity of human saliva, which is able to equilibrate demineralization and remineralization processes (2,13). The current study aimed to evaluate the accumulation of dental plaque after bleach-

ing, and did not try to evaluate any surface morphology alterations. Probably there is a corre-lation between them and for this reason further investigation are need to be done to elucidate this issue regarding possible morphological alterations of enamel bleached with 35% hydro-gen peroxide, which could alter the adhesion capacity of dental plaque. After vital bleaching when old fillings need to be changed, it is recommended to wait minimum two weeks after bleaching. Previous studies suggest that the shear bond strength of composite resins to enamel is reduced after exposure to 35% hydrogen peroxide. This may be because the free peroxide and oxygen radicals released from the bleaching products interfere with polymerization reaction, consequently reducing the bond strength. Alternatively, decrease of bond strength may be due to changes in mineral content of the enamel (17). Hy-pothetically it could be possible that due to these free radicals still present, the surface-free energy decreases and the capacity of adhesion, accumulation and maturation of dental plaque suffer modifications after bleaching. In order to minimize the subjectivity in evaluations, we used two different plaque in-dexes while determining the plaque accumulation (11). For more conclusive results, further studies should determine plaque accumulation after longer non-brushing periods.

CONCLUSIONS

With recognition of this short term in vivo study's limits, it can be said that bleaching with 35% hydrogen peroxide doesn't favor or accelerate dental plaque accumulation but un-der this study's circumstances post-bleaching plaque accumulation decreased.

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RESISTANCE TO IMATINIB AND SECOND GENERATION TYROSIN KINASE INHIBITORS, AN OVERVIEW

KINGA TATAR[1], HORTENSIA IONIȚĂ[1]

[1] University of Medicine and Pharmacy "Victor Babeş" Timişoara, Discipline of Hematology

Correspondence to:
Dr. Kinga Tatar, email: tatarkinga@yahoo.com.

ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative disorder, characterized by a specific chromosomal aberration, the Philadelphia [Ph] chromosome. The Ph chromosome is the result of a reciprocal translocation between the long arms of chromosomes 9 and 22, t (9; 22) (q34; q11). The molecular consequence of this translocation is a novel fusion gene, BCR-ABL, which encodes a constitutively active tyrosine kinase, implicated in pathophysiology and development of CML. Targeted therapy in the form of selective tyrosine kinase inhibitors (TKI) has transformed the approach to management of chronic myeloid leukemia (CML) and dramatically improved patient outcome to the extent that imatinib is currently accepted as the first-line agent for nearly all patients presenting with CML, regardless of the phase of the disease. Impressive clinical responses are obtained in the majority of patients in chronic phase; however, not all patients experience an optimal response to imatinib, and furthermore, the clinical response in a number of patients will not be sustained. Mechanisms of resistance to imatinib therapy have been extensively studied in the past decade, and novel molecules and therapeutic strategies have been evaluated in order to overcome resistance [1]. The introduction of second generation TKIs (SGTKI) in the past 4 years have at some extent addressed the issue of imatinib resistance (except the feared T315I mutation), however resistance occurs and the oncogenic BCR-ABL signal transduction is restored in some of the CML patients treated with SGTKIs leading to clinical disease resistance. In contrast with imatinib resistance extensively explored in the past years, the mechanisms involved in the second generation TKI resistance are a more recent topic of very high interest. The molecular pathogenesis of resistance against novel tyrosine kinase inhibitors, nilotinib, or dasatinib in CML patients is best understood based on mutations within the ABL-kinase domain. However, in about 50% of patients, clinical resistance so far cannot be linked to known mutations. Mutation-independent resistance development is imparted by a multifactorial array of mechanisms. Along with the understanding of the complex mechanism involved in resistance different alternative therapeutic strategies started to be evaluated: clinical studies now focus on dose modifications, drug scheduling, optimized inhibitors, and drug combinations aiming to prevent resistance development.[2] In this review article we intend to make an overview of the most recent data addressing the issue of tyrozin kinaze inhibitor resistance and strategies of overcoming them.

Key words: Tyrozin kinaze inhibitors, chronic myeloid leukemia, resistance, mutations

INTRODUCTION

The development of Bcr-Abl1 tyrosine kinase inhibitors (TKIs), first attempted over a decade ago, has revolutionized the treatment of chronic myeloid leukemia (CML). The TKI imatinib called "the magic bullet" has dramatically changed the natural history of patients with CML, who had been doomed to

perish within 5 years to 6 years after diagnosis. The impact of imatinib on the outcome of patients with CML is so great that many of them are predicted never to transform to the accelerated phase (AP) or blast phase (BP) in their lifetimes; these individuals will live with a chronic disease that requires continuous therapy for its adequate management. For the first time, it is possible that many patients may die with CML but not because of CML. Notwithstanding this remarkable achievement and the rapidity with which it has been accomplished, a considerable proportion of patients treated with imatinib will develop resistance or intolerance to the initial TKI and will require further therapy. Recent research efforts have been devoted to developing novel TKIs capable of overcoming the mechanisms of resistance to imatinib therapy. [3]

Resistance to imatinib

Frequency:

A recent analysis of the IRIS trial involving all enrolled patients after 7 years of follow-up has revealed EFS of 81%, transformation-free survival (TFS) of 93%, and an estimated overall survival (OS) of 86%. Although the estimated best observed rate of CCyR is 82%, only 317 (57%) of the 553 patients randomized to the imatinib arm remain in CCyR at 7 years. In this group, the major molecular response (MMR) rate was 86% [3] In spite of the high response rates, the IRIS data highlight the fact that a sizeable proportion of patients either fail to respond to imatinib therapy r achieve only a suboptimal response. Another study evaluated the efficacy of imatinib in 204 adults with newly diagnosed CP CML who were treated with imatinib at a single institution between 2000 and 2006. At 5 years, the CCyR was 83% and MMR was 50%. An intention-to-treat analysis showed both the estimated OS and EFS to be 83%. At 5 years, 25% of patients had discontinued imatinib because of either a suboptimal response or toxicity. [3]

Clinical implications

The clinical translation of resistance is designated by the commonly known term of treatment failure. There are generally accepted criteria for defining failure, and these criteria are becoming stricter along with more data becoming available. An expert panel on behalf of European LeukemiaNet had defined for the first time in 2006 the criteria for imatinib treatment failure as not meeting therapeutic targets after certain months of treatment. At that point failure was defined as: no HR at 3 months, less than CHR or no CyR at 6 months, less than PCyR at 12 months and no CCyR at 18 months. Losses of CCyR, CHR or occurrence of highly imatinib insensitive mutations were also considered as failure. [4] In this context "failure" means that continuing IM treatment at the current dose is no longer appropriate for these patients, who would likely benefit more from other treatments. Criteria for "suboptimal response" were also provided, with the significance that the patient may still have a substantial benefit from continuing IM, but that the long-term outcome of the treatment would not likely be as favorable. Based on the review of information that became available in the meanwhile, the same group revised these definitions of failure at the end of 2009, with establishing even stricter targets. Thus if a patient did not achieved CHR at 3 months is already included in the failure category.[5]

Mechanisms

Although the mechanisms driving primary resistance to imatinib remain unclear, much has been revealed about the underlying mechanisms of secondary resistance. These mechanisms are multifactorial but can be categorized into two broad groups; BCR-ABL dependent and BCR-ABL-independent. The most commonly identified mechanism of imatinib-resistance involves point

mutations in the ABL kinase domain of the BCR-ABL fusion protein. Point mutations within the kinase domain will lead to suboptimal binding or complete blockade of imatinib from its binding site. [6] There are nearly 100 described mutations of the fusion BCR-ABL tyrosine kinase) . BCR-ABL mutations have been reported in patients with secondary resistance at a frequency ranging from 42% to 90% in different studies [7,8]. The vast majority of identified mutation generally fall within four regions of the kinase domain, including, the ATP-binding loop (P-loop), contact site (e.g., T315 and F317), SH2 binding site (e.g., M351) and A-loop [9]. BCR-ABL mutations that impair imatinib binding while still enabling ATP binding, or that alter the specific protein conformation required for imatinib binding, are selected in the presence of imatinib. In the absence of imatinib, these mutations do not confer a growth advantage. [10] One particular mutation, insensitive at every approved therapy is the T315I mutation. T315I mutation occurs with substitution of threonine by a bulky isoleucine at the highly conserved 'gatekeeper' residue within the kinase domain. This substitution inhibits TKIs from access to their target, which is located deep in the hydrophobic pocket of the ABL kinase active site [11]. This mutation, which has been described in 4–15% of patients with imatinib resistance [12,13], is most frequently detected in patients with CML who progress to advanced disease while on imatinib, and may likely convey a poor outcome and inferior survival [14]. As the T315I mutation leads to resistance to all currently approved TKIs, several strategies have been devised to overcome this resistance. These include optimization of direct inhibition of the BCR-ABL kinase, increased degradation of the BCR-ABL oncoprotein, and inhibition of BCR-ABL protein formation via interruption of transcription, protein synthesis or post-translational modification of this tyrosine kinase.[15] The different imatinib-resistant mutations occur at varying frequencies and confer distinct levels of imatinib resistance. In the past years there were generated databases where the potential level of in vitro resistance induced by a certain mutations was recorded. This data are determined by in vitro cell proliferation assays. Although there are voices contesting their in vivo accuracy, these databases are a useful tool for the clinician in order to take the adequate therapeutic decision when identifying a BCR-ABL mutation in a patient. Of all mutations identified to date, the most frequently occurring (30% – 40% of mutations) are those of the P-loop which have been demonstrated to confer high levels of resistance to imatinib. In kinase assays, P-loop mutants were found to be 70- to 100-fold less sensitive to imatinib vs. native BCR-ABL, and were approximately 10-fold less sensitive in cell proliferation assays [16]. An additional mechanism of BCR-ABL-dependent imatinib resistance may occur through increased production of BCR-ABL, either at the genomic (gene duplication) or transcript (overexpression) level. In-situ hybridization studies have detected cells containing multiple copies of the BCRABL gene in some patients. Gorre et al., showed genomic amplification of BCR-ABL in 3 of 9 patients with imatinib-resistant CML [17]. In another study, overexpression of BCR-ABL was detected at the mRNA level in 4 of 37 imatinib-resistant patients [18]. Although it occurs more commonly in advanced disease, patients in CP do occasionally develop disease progression despite adequate binding of the imatinib to the BCR-ABL tyrosine kinase [15]. BCR-ABL induces transformation of hematopoietic stem cells through activation of multiple downstream substrates. Therefore, constitutive activation of one of these downstream signaling molecules could result in activation of the pathway regardless of BCR-ABL inhibition, thereby resulting in imatinib-resistance. The SRC family kinases (SFKs) may be one such example of substrates and essential mediators of BCR-ABL signaling [19, 20]. Downstream

mutations can lead to over-expression of c-Myc and other dominant oncogenes which are capable of driving pro-survival signaling independent of BCR-ABL These signaling molecules are known been implicated in the development of late-stage CML, as well as BCR-ABL-independent imatinib resistance [19, 21-24]. Another, more recent preclinical study, demonstrated that the phosphorylation of SH2-SH3 region of BCR-ABL by SFKs is required for full oncogenic activity, and therefore CML pathogenesis [26]. Studies have demonstrated that CML cell lines exhibiting imatinib-resistance unrelated to BCR-ABL over express LYN and HCK and that coinhibition of SFKs and BCR-ABL in these cells was shown to induce an enhanced apoptotic response [27,28]. Donato et al., showed that imatinib effectively reduced activation of both BCR-ABL and SFKs in specimens derived from patients with imatinib-sensitive CML, while it reduced BCRABL kinase activation but had no effect on SFK activation in samples from resistant patients [29]. These studies indicate that SFK activation can become independent of BCR-ABL in some forms of imatinib-resistant CML, and suggest that dual inhibition of SFKs and BCR-ABL would be clinically beneficial for patients who develop such resistance. An additional means of BCR-ABL-independent resistance involves mechanisms that act to decrease intracellular concentrations of imatinib. Studies in a mouse model of leukemia showed that tumors that were resistant to imatinib in vivo could regain their imatinib sensitivity in vitro, suggesting involvement of an extraneous factor in the development of resistance [30]. The plasma protein a-1 acid glycoprotein (AGP) was found to bind imatinib at physiologic concentrations in vitro, blocking inhibition of the ABL kinase in a dose-dependent manner. Subsequent clinical studies have shown that plasma AGP binding correlates with clinical responses to imatinib, although a causative role for AGP in human imatinib resistance has yet to be definitively established [31,32]. Another recently studied potential cause for inadequate imatinib response is related to pharmacokinetics of the drug and oral bioavailability. From this perspective, different factors impacting drug intake (adherence), plasma protein binding and methabolization via CYP3A4 might result in inadequate drug concentration thus leading to resistance. [38] In vitro studies have also provided evidence that increased expression of multi-drug resistance Pglycoprotein (Pgp) may contribute to imatinib resistance [33-35]. This protein is known to increase cellular efflux of an array of anticancer drugs reducing their overall effectiveness [36]. Imatinib is a substrate for Pgp, and expression of this protein has been shown to mediate imatinib resistance [35]. Conversely, decreased drug influx, mediated by the OCT-1 protein, can also impact imatinib sensitivity [37]. A recent study showed that intracellular uptake and retention (IUR) of imatinib strongly correlated with the IC50 in 25 untreated CML patients. Inhibition of OCT-1 reduced the IUR and decreased interpatient IC50 variability.

Therapeutic approach after identifying resistance to imatinib

For patients with chronic myeloid leukemia who become or are inherently resistant to imatinib, therapy, including dose escalation, several important factors must be considered when deciding which strategy to attempt next. The second-generation tyrosine kinase inhibitors (TKIs) dasatinib and nilotinib offer improved potency and a high likelihood of success for these patients. Overall, the efficacy data are comparable for these two agents, and so physicians should consider the BCR-ABL mutation profile and the patient's history to make an educated decision on the best choice. Only a few BCR-ABL mutations seem to be less responsive to either nilotinib or dasatinib and it is recommended to choose the second-line TKI that has shown clinical activity against the specific mutation in these cases. For patients with all other mutations, and for

patients with no mutations, it is recommended to choose the second-generation TKI based on the patient's disease history. It is important to choose an agent that minimizes the likelihood of exacerbating the patient's past tolerability issues to imatinib, or comorbid conditions. Authors from MD Anderson have recently proposed a treatment algorithm for imatinib-resistant patients based on BCR-ABL mutation status and patient history. In the choice of the second generation TKI the first criteria taken in consideration is the mutational status. For patients with mutated clones the choice should be made based on the in vitro susceptibility .For patients without mutation the choice is recommended to be made based on patient history and existing comorbidities [39]. A number of analyses have been conducted to determine the response rates of patients with various BCR-ABL mutations to second-generation TKIs. A recent study of 581 imatinib-resistant or -intolerant patients from the dasatinib dose-finding study (35% with baseline mutations) examined the correlation between baseline imatinib-resistant BCR-ABL mutations and response to dasatinib 70mg twice daily in CML-CP.[40] Dasatinib was efficacious regardless of most mutations and results did not differ significantly across dasatinib doses. Overall, only a subgroup of patients showed mutations that were less sensitive to dasatinib (Q252H, E255K/V, V299L and F317L). A recent analysis of imatinib-resistant CML-CP patients was conducted to assess patients for the occurrence of baseline BCRABL mutations and to determine the impact of those mutations a fter 12 months of nilotinib therapy.[41] Hematological and cytogenetic response rates to nilotinib were similar regardless of the presence or absence of most mutations. However, it was observed that patients with E255K/V, Y253F/H or F359C/V mutations had less favorable outcome with nilotinib therapy.

These studies show that patients without mutations before second-generation TKIs, and most patients with mutations, have similar response and progression rates on nilotinib or dasatinib therapy.[40,41] These results also suggest that very few patients show baseline mutations in BCR-ABL, subsequent to imatinib resistance, that have overlapping resistance to both nilotinib and dasatinib. The T315I mutation is the least responsive mutation to imatinib, dasatinib or nilotinib with median inhibitory concentrations (IC50s) of 46400, 4200 and 42000 nM, respectively. [42] For patients with the T315I mutation, switching to an investigational agent may be the best option. Investigational agents, such as MK-0457, ON01910, ON12380, XL-228 and PHA739358, which target regions outside the ATP-binding site of BCR-ABL, may be more effective against the T315I mutant. [43]

Resistance to second generation TKIs

The commercially available second generation TKIs (2G-TKI), dasatinib and nilotinib, are both effective in imatinib failure. Dasatinib, a dual SRC/ABL kinase inhibitor that binds to the ABL kinase domain irrespective of the configuration of the activation loop also inhibits KIT and PDGFR receptors, as well as being 325-fold more potent than imatinib against unmutated BCRABL1 in vitro. Nilotinib, an orally available aminopyrimidine derivative, is a more specific inhibitor of ABL kinase binding to the inactive-closed conformation, and also inhibits KIT and PDGFR receptors and has been noted to have a 20-fold greater potency than imatinib (15).

Recommendations for optimal responses to 2G-TKI following imatinib failure were recently issued by the European Leukaemia Net.

Oral bioavailability

From a clinical perspective, in order for a drug to be effective it is required to reach its target. SGTKIs are oral medication and influenced in the first instance by the adherence or compliance of the patient to therapy. Thus lack of compliance to the

second generation TKIs represents a potential cause for treatment resistance.

Multi Drug Resistance gene

Nilotinib has been identified as a substrate of P-gp (the product of the MDR-1 gene) in nilotinib-resistant cell lines [44] and of ABCG2 [45], however, resistance through ABCG2 may not be observed at clinically relevant levels of nilotinib [45, 46]. In vitro studies suggest that cellular delivery of dasatinib is predominantly a passive process, unlike imatinib [47], and is also limited by active efflux because of ABCB1 [48] and ABCG2 [47], but of interest, no significant difference was found in the amount of dasatinib unabsorbed in the gastrointestinal tract in ABCB1 knockout and wild-type mice [49].

OCT1-human organic cation transporter

The human organic cation transporter (hOCT-1; SLC22A1) has been advocated as a significant factor affecting intracellular drug availability through inhibition of imatinib influx [50, 51], and polymorphisms of OCT-1 may alter the entry of imatinib into cells through this transporter mechanism. Importantly, neither SGTKI's cellular uptake is significantly affected by OCT-1 activity [50], which in turn exhibits less interpatient variability.

Examining drug influx and drug efflux properties at presentation prior to therapeutic intervention may give insight from the start of therapy about an expected response and potentially provide a strategy for the use of a particular TKI in order to achieve the best outcome.

SRC overexpresion

An increase of LYN expression has accompanied failure of nilotinib treatment in CML patients [52].

Targeting both BCR-ABL1 and LYN kinases may be required in resistant CML, and dasatinib has also been shown to be effective in imatinib resistance consequent to BCR-ABL1-independent LYN activation [53].

Quiescent cells

Dasatinib, although able to induce significant inhibition of CrKL phosphorylation in CD34+CD38- cells in comparison to no effect with imatinib and to inhibit an earlier progenitor population, remains ineffective in eradicating the most primitive QSC population (cells that retain maximal carboxyfluorescein succinimidyl ester fluorescence [54]. Similarly, the quiescent fraction shows resistance to nilotinib, and furthermore, is noted to increase with the combination of nilotinib and imatinib secondary to antiproliferative and nonapoptotic effects [55].

BCR ABL amplification

Cells expressing a high level of BCR-ABL1 have been observed to be far less sensitive to imatinib and more rapidly yield imatinib-resistant mutant subclones than cells with low BCR-ABL1 expression levels. Similarly, resistance to nilotinib in vitro has also been found consequent to BCR-ABL1 overexpression in vitro [56].

Mutations

Although most of the clinically relevant mutations are inhibited by dasatinib and nilotinib, with the exception of T315I [57], the presence of existing mutations after imatinib failure, as well as development of new mutations on a subsequent second TKI is naturally a potential source of resistance to successive TKI [58-61]. The influence of baseline BCR-ABL1 mutations on response to nilotinib in patients with imatinib-resistant CML in chronic phase has shown an inferior outcome in patients who harbored mutations that were less sensitive to nilotinib in vitro (Y253H, E255V/K, and F359V/C; [41]. Recently, the selective pressure of sequential TKI therapy has been assessed in the outcome of imatinib resistant patients already harboring imatinib-resistant kinase domain

mutations subsequently treated with an alternative TKI on a second or even third occasion. Results showed that 83% of cases of relapse after an initial response were associated with the emergence of newly acquired mutations [62]. The T315I mutation was most commonly implicated with a frequency of 36% [62]. The inability to achieve a sustained cytogenetic response could in part be as a consequence of the development of new therapy-resistant kinase domain mutations as patients are exposed to sequential TKIs, although some of the arising mutations were reported as having a relatively good in vitro sensitivity to the concurrent TKI [63].

In summary, the consequence of identifying a mutation remains unclear and seems relevant only according to the disease phase and response, with a greater impact in advanced phase CML in which the mutated clone may be responsible for disease progression, but less certain in cases of on-going response to TKI therapy. Resistance mechanisms may be overcome with imatinib dose escalation, alternative therapy with a 2G-TKI to which the mutant has documented sensitivity, withdrawing TKI therapy to allow the mutant clone to recede, as well as non-BCR-ABL1-dependent therapies [1]. It has been suggested that some BCR-ABL mutations play no causal role in resistance. However, approximately half of the patients who commence SGIs after imatinib therapy have detectable imatinib-resistant BCR-ABL mutations. For patients commencing treatment with a second generation TKI after imatinib cessation, clinical trials have demonstrated similar responses for patients with or without mutations, except for T315I for which neither drug is active. This mutation demonstrates cross-resistance to imatinib, nilotinib, and dasatinib. However, a closer examination of responses to SGI therapy for individual mutations has identified a limited number, other than T315I, that are less sensitive to either nilotinib or dasatinib. Furthermore, in vitro studies have identified mutations that confer a degree of insensitivity or resistance, but some questions related to the clinical relevance of these in vivo examinations still remain: How well do the problematic mutations identified by in vitro studies correlate with those identified by clinical studies? Moreover, does the in vitro sensitivity of mutations provide a reliable indication of the probable response to SGIs? Undoubtedly, in vitro sensitivity of imatinib-resistant mutations can be a useful guide when considering an increased imatinib dose. In a recent publication from Susan Brandford, there were assessed BCR-ABL mutations in the context of their impact on response after a change to SGI therapy by an overview of the available clinical data. [10]. the mutation status may contribute to therapeutic decisions after imatinib failure or indeed after failure of an SGI. In the publication it was assess the frequency that mutations conferring a degree of clinical insensitivity to SGIs are detectable at the time of imatinib cessation. These are collectively referred to as SGI clinically relevant mutations. The authors also examine whether the disease phase influences their frequency and the occurrence of multiple mutations in imatinib-treated patients and the extent to which disease phase influences their detection. In this cohort of patients with mutations at imatinib cessation and/or SGTKI commencement, 43% had SGI clinically relevant mutations, including 14% with T315I. The frequency of SGI clinically relevant mutations was dependent on the disease phase at imatinib failure. The clinical data suggest that a mutation will often be detectable after imatinib failure for which there is compelling clinical evidence that one SGI should be preferred.

CONCLUSIONS

Targeted molecular therapy has afforded exceptional clinical responses in the majority of patients with CML to the extent that therapeutic regimens have centered on the achievement of a MMR, early within the start of therapy. As most

will continue on imatinib in CCyR, the emphasis has diverted to overcoming imatinib resistance and the generation of alternative TKI engineered to surmount these clinical challenges. The cause of resistance to TKI therapy is likely to be multifactorial, but ultimately the clinical response is influenced in most part by leukemia-related factors and the phase of the disease. Further investigation into the underlying causes of TKI resistance remain mandatory in order to best direct appropriate therapy in this subset of patients and preclinical studies need to be validated by clinical evidence. Studies on new drugs targeting different pathways other than BCR-ABL are ongoing to improve the clinical results. With no currently approved effective treatment for CML resistant to BCR-ABL kinaze inhibition, molecularly-based, targeted drug development has focused on several strategies to overcome resistance. Agents which overcome the T315I mutation, as well as native BCR-ABL, via several mechanisms, including increased degradation of BCR-ABL, optimization of direct inhibition of the BCR-ABL, kinase, inhibition of BCR-ABL-mediated cell growth via interruption of the BCR-ABL-mediated transcription, protein synthesis or post-translational modification, leading to decreased proliferation and malignant cell death have been intensively studied in the past years.[64]

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RISC FACTORS FOR PULMONARY TUBERCULOSIS IN AN ENDEMIC AREA

ADRIANA SOCACI[1], VOICU TUDORACHE[2]

[1] V.Babeş" Clinical Hospital, Pneumophthisiology Ambulatory Center, Timişoara,
[2] V.Babeş" Clinical Hospital, Pneumophthisiology Department, Timişoara,

Correspondence to:

SOCACI ADRIANA, mobil:0723705832, e-mail: adriana_socaci@yahoo.com.

ABSTRACT

Objectives: Assessment of TB-risk factors in an endemic area. Material and methods: Prospective study of exposure to a variety of risk factors before and during active pulmonary tuberculosis (TB). The study group consisted of 427 teenage and adult subjects diagnosed with TB, confirmed by TB culture, between 1 January – 31 December 2009, in the Timis County. Information regarding potential TB-risk factors was collected by means of a questionnaire together with the data existing in the county TB records. Results: The main risk factors in TB were: chronic smoking (24.59%), chronic alcoholism (19.2%), socio-economical status – the absence of any medical insurance (25.06%), diabetes mellitus (6.09%), HIV status (2.34%) and cohabitation with a relative infected with TB (3.05%). Conclusions: When the incidence of exposure is taken into consideration, the most important factors in developing TB in the Timis County were chronic smoking, poor socio-economical status (lack of medical insurance), chronic respiratory diseases and, last but not least, diabetes mellitus.

Key words: mutations pulmonary tuberculosis, risk factors, exposure.

INTRODUCTION

Pulmonary tuberculosis (TB) remains a major global health problem when we consider the 8 – 10 million new cases and the 1.7 million deaths that occur every year; besides one third of the world population is infected with Mycobacterium tuberculosis.

In our country, TB continues to have a major impact despite the implementation of the PNCT strategy. The Timis County is the region where the incidence of TB still holds values that are above those at national level.

Starting from these facts, the authors have analyzed the main risk factors involved in the occurrence of TB in the region.

MATERIAL AND METHODS

The authors conducted a prospective study focusing on the exposure to a variety of risk factors before and during active TB. The study group consisted of 427 teenage and adult patients diagnosed with TB (new and relapsing cases). Diagnosis was confirmed by TB cell culture, between 1 January – 31 December 2009, in the Timis County. A new case is a patient who has never received any treatment for TB or who was on anti-TB medication for less than a month. Relapse is defined as a patient who has been previously treated for TB, the treatment was considered complete or the patient was declared cured, and has subsequently been

diagnosed positive for TB after a bacteriological exam (swab or culture). The study was completed by using a questionnaire for collecting the information on potential TB - risk factors as well as the data registered in the county TB records.

The potential risk factors taken into consideration were: chronic smoking, chronic alcoholism, socio-economical status (health insurance), chronic respiratory diseases, diabetes mellitus (DM), HIV status, and cohabitation with a relative who has TB.

RESULTS AND DISCUSSION

The main profile of our study group was done according to the category of TB patients included in the study: new case and relapse. Of the 427 patients included in the study, 289 were men (67.68%), and the M:F ratio was 2.09:1. As for the category of TB patients, 316 (74%) were new cases and 111 (26%) were relapses. The age interval was 15-65+ years for the new cases, and 25-65+ years for relapses; the highest incidence was recorded for the age group ≥ 55 years, both for the new cases (27.52%) and for relapses (36.03%) (Table I).

Table I. Main profile of study group

Characteristics	Category – TB patients		
	New cases (316) n (%)	**Relapses (111) n (%)**	**Total (427) n (%)**
Age interval	15-65+ years	25-65+ years	**15-65+ years**
Gender ratio(M:F)	1.98:1	2.47:1	**2.09:1**
Sex:			
Male	210 (66.46)	79 (71.17)	**289 (67.68)**
Female	106 (33.54)	32 (28.83)	**138 (32.32)**
Age groups			
≤24 ani	**53 (16.77)**	**-**	**53 (12.41)**
25-34 ani	**52 (16.45)**	**18 (16.22)**	**70 (16.39)**
35-44 ani	**59 (18.67)**	**21 (18.92)**	**80 (18.74)**
45-54 ani	**65 (20.57)**	**32 (28.83)**	**97 (22.72)**
≥55 ani	**87 (27.52)**	**40 (36.03)**	**127 (29.74)**

Table II Risk factors associated with TB

Risk factors	Category of TB patients		
	New cases (316) n (%)	**Relapses (111) n (%)**	**Total (427) n (%)**
Medical insurance			
Insured	237 (75)	83 (74.77)	**320 (74.94)**
Uninsured	79 (25)	28 (25.23)	**107 (25.06)**
Chronic alcoholism			
Yes	51(16.14)	31 (27.93)	**82 (19.2)**
No	265 (83.86)	80 (72.07)	**345 (80.8)**
Chronic smoking			
Yes	67 (21.2)	38 (34.23)	**105 (24.59)**
No	249 (78.8)	73 (65.77)	**322(75.41)**
Cohabitation with a TB relative			
Yes	**3 (0.95)**	**10 (9.01)**	**13 (3.05)**
No	**313 (99.05)**	**101 (90.99)**	**414 (96.95)**

TB – risk factors. The following risk factors were assessed: socio-economical status (inferred from the patients' medical insurance), chronic smoking and chronic alcoholism, and cohabitation with a relative that has TB (Table II).

The analysis of the data showed the impact of each risk factor as follows: seventy-five per cent (75%) of the new cases and 74.77% of the relapse cases had medical insurance, which shows that over 25% of the TB patients lacked such insurance; one third of the latter were social cases (homeless persons). Chronic alcoholism was higher in relapse cases (27.93%) versus new cases (16.14%), chronic smoking was also higher in relapse cases (34.23%) versus new cases (21.2%).

Cohabitation with a diseased relative (TB) was lower both in relapse cases (9.01%) and in new cases (0.95%); this low percentage might be correlated with the reluctance to admit connection to a former TB patient due to the stigma of this disease.

Comorbidity as a risk factor in TB. Several types of comorbidity were followed in our study: chronic respiratory diseases (asthma and chronic obstructive pulmonary disease), diabetes mellitus (type I – insulin-dependent DM and type II – non-insulin-dependent DM), as well as the HIV status (Table III). The three types of comorbidity do not represent only a TB-risk factor but, if not treated accordingly, they can even determine a negative development of active TB. In our study, chronic respiratory disease was associated with TB in 11.24% of the cases (7.9% new cases, 20.72% relapse cases). Diabetes mellitus also represented an important associative TB-risk factor, with an overall percentage of 6.09% (1.87% - DM type I; 4.22% - DM type II). According to the category of patients, DM was present in 6.64% of the new cases (1.58% - DM type I; 5.06% - DM type II) and 4.5% of relapse cases (2.7% - DM type I; 1.8% - DM type II). HIV was present only in the new cases (3.16%) with an overall incidence of 2.34%.

Table III Comorbidity associated with TB

Comorbidity (risk factors)	Category of TB patients		
	New cases (316) n (%)	Relapses (111) n (%)	Total (427) n (%)
Chronic respiratory disease			
Yes	25 (7.9)	23 (20.72)	**48 (11.24)**
No	291 (92.1)	88 (79.28)	**379 (88.76)**
Diabetes mellitus			
DM type I	5 (1.58)	3 (2.7)	**8 (1.87)**
DM type II	16 (5.06)	2 (1.8)	**18 (4.22)**
No	295 (93.36)	106 (95.5)	**401 (93.91)**
HIV infection			
Yes	**10 (3.16)**	-	**10 (2.34)**
No	**306 (96.84)**	**111 (100)**	**417 (97.66)**

CONCLUSIONS

The present study revealed an important aspect of chronic smoking and alcoholism as TB-risk factors both due to the direct negative effects facilitating the development of active TB and due to their indirect effects manifested in the patient's behavioural changes and refusal to follow medication. Besides chronic smoking and alcohol consumption, the socio-economic factor is another important TB-risk factor, especially as the three factors are often associated, thus enhancing the risk of developing active TB in an endemic area. Comorbidities, such as chronic respiratory disease and diabetes mellitus, also have a major importance as potential risk factors in the development of active TB in an endemic area. In order to be able to control TB one should understand the complexity of risk factors and the socio-economical

dimensions of the disease in a certain community and, consequently, take appropriate and constant measures. As the study shows, three of the risk factors are related to the patients' needs (socio-economical status) and their vices (alcoholism, smoking), factors that can be controlled by sustained measures at community and social level. The types of comorbidity involved as TB-risk factors can also be controlled by proper healthcare measures. Our study represents only a shy attempt to reveal potential TB-risk factors in the area; such studies should be carried out more often especially as we live in an area with high TB levels despite all the measures taken according to the National TB Control Strategy.

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PROMOTING ORAL HEALTH EDUCATION THROUGH COMMUNITY EDUCATION PROGRAMS FOR CHILDREN

ATENA GĂLUŞCAN[1], DANIELA JUMANCA[1], PODARIU ANGELA[1], OANCEA ROXANA[1], POPOVICI RAMONA[1], SAVA-ROŞIANU RUXANDRA[1], ROŞU ANITA[1], DURAN AURELIAN[2], MUNTEAN CĂLIN[2], BUNESCU ADRIAN[2]

[1] Department of Preventive, Community Dentistry and Oral Health, Faculty of Dentistry, University of Medicine and Pharmacy "Victor Babes" Timişoara
[2]PhD Student UMF "Victor Babeş" Timişoara

Correspondence to:
Atena Galuscan, DMD, PhD, Lecturer, Department of Preventive, Community Dentistry and Oral Health, Faculty of Dentistry, University of Medicine and Pharmacy "Victor Babes" Timisoara, E-mail: atedent@yahoo.com

ABSTRACT

Oral health means much more than having healthy teeth, because of its implication on the general health status, social status and the quality of life for each individual. It has been observed that generally, health education and especially oral health education, starting from early childhood has benefic effects on the future teenager and adult. Acces to information related to this subject plays an important role in education. This paper tries to establish some principles which set the base for an educational program and to evaluate different methods that are used in an oral health education program.

Key words: oral health, educational programs, children, school

INTRODUCTION

Oral disease can be broadly prevented and the challenge nowadays consists in creating opportunities and conditions to allow individuals and society in general to enjoy good oral health. Despite the progress in the field of techniques and materials which have made dental treatment more efficient and acceptabile, this alone will not eradicate oral disease. Especially in countries with low or medium income, the total cost for medical inssurance would outgrow the whole health budget. This is why one has to find new ways of preventing oral disease and for oral health promotion at community level. Oral health programs represent a "succession of undertaken activities to improve one or more aspects of the oral health status for a populational group" [1]. WHO has couched numerous preventive and control strategies for oral disease:

There are different methods to create an oral health program, but all of them have to consist of the following stages:

1. Identifying the health problem through a scientific study which evaluates treatment needs

a. Data regarding the health problem – determins the gravity and extent of the condition. Gathers informations through clinical examination, epidemiological data like caries indexes, dental plaque indexes, gingival or parodontal indexes. Afterwards the data is statistically analyzed. Clinical examination has to be realized only by professionals for the data accuracy [2, 3].

b. Demographic data, regarding the profile of the community – obtained through interviews and questionnaires. This profile includes the following: number of individuals, geographic distribution, density of the population, ethnic criteria, economic and social environment, living conditions, addressability to medical care services, schooling system.

c. Data regarding educational status – obtained through interviews or questionnaires. This refers to health knowledge, life style and diet. Also, to evaluate the incidence and distribution of oral conditions, a study can be carried out regarding existing dental programs in the community.

One who wants to create a health program at community level has to understand the way politics and decision making works at this level. Following areas have to be explored:

- Who are the financial leaders (bankers) and political leaders (city mair, city council)?
- Who does politics in the community?
- How is the community organized?
- Which attitude do political leaders have towards oral health and community programs?

2. Defining the target group

The target group is punctually centered on a health program and can be represented by preschool children, pupils (primary and secondary school), teenagers, highschool pupils, adults (divided into age groups), pregnant women, children with disabilities, institutionalized elderly, etc. If the group consists of children one has to also pick up the secondary receptors, represented by the parents, educators who are actively involved in the education process [4]. From the target group, a witness (control) group and at least one active group has to be selected, the groups being comparable as dimension and homogeneity.

3. Establishing priorities

Establishing priorities identifies the most important health problem, so the program can aim the individuals who need the most attention. For example, if a problem affects a large number of people this means it will have priority over a problem that affects a smaller number of persons. On the other hand a severe condition that affects a small number of individuals has priority over a simple condition that affects a larger group. If the health issue is represented by dental caries, there usually is more than one affected group. Following populational groups are associated with high risk for dental conditions: preschool children and pupils, people with disabilities, chronic disease patients, elderly, pregnant women, low income families. The moment the target group has been established, considering the dental condition that has to be solved, the type of program has to be decided.

4. Establishing strategy and implementing methods

Priorities, objectives and implementing methods represent the strategy of the program. The methods for education are choosen considering the identified problem in the evaluation stage [5, 6]. For example, after identifying dental caries as a problem among children at school age in community X, the goal of the program would be to "improve oral health of children at school age from community X" an objective example could be: "Until 2010, 90% of children at school age (6-7 years of age) from community X won't loose any teeth because of decay and at least 40% will be caries free." This type of program takes into consideration measurable results, so that at the end of the program both the evaluator and the community know that it was efficient.

The next step would be the activity program which will help to put the objectives into practice [7]. The activity program has three components:

• What needs to be done?

• Who will do it?

• When will it be done?

Once this point is reached, the available resources and possible constraints have to be taken into consideration.

5.Identifying and obtaining material, financial and human resources

The one responsible for carrying out the program has to ask the following questions regarding the available resources in the community, resources necessary for implementing the program [2].

6.Monitorizing and evaluating the program

Once implemented, the program needs to be continuosly supervised. Success depends on monitorization of [8, 9]:

• Activities (how well are objectives achieved)

• Work force (how well do the employees fullfil their work tasks)

• Equipment (how well does it work) and

• Facilities (are they adequate)

The most efficient method to decrease prevalence and incidence of oral conditions is to conduct oral health programs in schools [1, 10].

The major objectives of such programs are:

• Increasing the number of children who benefit from health services [11]

• Increasing the number of health centers in schools [12]

• Improving acces to school dental services for children coming from low income families

• Decreasing the percent of children with untreated dental caries [13]

• Decreasing the percent of children with caries on deciduous and/or permanent teeth [14]

• Increasing the number of informed children who are capable to control dental plaque and selfdiagnose,

• Increasing the number of children who have proper dental hygiene.

School health services that also offer dental services, have the advantage to outgrow existent barriers that restrain children's acces to health services such as: lack of interest, lack of education in the family environment, distance/time and social economic status [15]. Informing the parents or legal guardians is mandatory, because only after obtaining their consent one can take all the measures to improve and maintain oral health for these children. In order to achieve the wanted results, implication of community centres along with school centres would contribute to improving the level of education for families and the acces to dental services. For a successful implementation of a school program it is necessary to create a partnership between the target group (children with their parents or legal guardians), the departments involved in offering dental services, school personell and local dicision makers. There have to exist optimal relations between the functions and objectives of health programs, so that any inequality can be ruled out from the beginning.

The quality of oral health strategies can be evaluated using the following set of criterias [16]:

• Commissioning: strategies have to offer individuals and community in general the possibility to assume more power on personal, social, economic and environmental factors which affect their oral health.

• Participation: Medical staff involved in oral health issues has to encourage active implication of key persons, who play a decisional role in planning, implementing and evaluating strategies.

• Holistic approach: Initiatives have to improve health from the physical, mental and social point of way and to focus on conjoint conditions and risk

factors that can influence both general and oral health status.

• Equitability: strategies have to be guided by equity and social justice and pursue the elimination of unequalities in health assistance.

• Evidence: oral health interventions have to be developed based on solid knowledge regardind the practice and efficiency of the implemented program.

• Sustainability: individuals and the community have to maintain and sustain the program once the intial funds peter.

• Multiple strategies: strategies have to use several ways to promote oral health improvement.

• Evaluation: Sufficient resources and adequate methods have to be directed to the monitorization and evaluation of strategies.

The implementation of the National Program for Caries Prevention in Romania through Fluoride Solution Mouth Rinsing fulfilled these principles and specific objectives necessary to attain the objectives of a prophylaxis program for children.

The number of pupils who participated in the program was: 12 400 (Iasi), 4012 (Timisoara), 20000 (Constanta).

The following important changes in the ore-dental health status of the children included in the program were obtained [17]:

a) Caries prevalence in decidual teeth registered a 3,8% decrease;

b) The DMF-d index for 6 year old children decreased by 10,9% from a value of 3,92 in 1995 and by 23,13% compared to 1992;

c)The percent of caries free decidual dentition maintained a value of 14%, but the percent of the level 4 severity decreased significantly from 61% in 1992 to 20,8% in 2005.

d) Dental caries prevalence in permanent teeth of 12 years old children registered a decrease by 32,26% in 2005, compared to 1995

e)The DMF-D index for 12 years old children indicated a value of 2,35 in 2004 and 2,27 in 2005. This value is 16% lower than the one in 2000, 33,23% lower compared to 1995 and 44,63% lower than 1992.

f) The percent of caries free 12 years old children increased from 10% in 1992 to 28,3% in 2005.

Improving health in general and especially oral health, is due to the increasing acces to information regarding sanogen attitudes, as well as the changing attitude of the educators (parents and teachers) and pupils towards oral health [4]. The results of a comparative study designed by Danila-Petersen et. all. regarding, habits, knowledge and attitudes of mothers and teachers towards oral health, during 1993-2003, proves a real improvement of the general situation although the knowledge level is still diminuished [18, 4, 20]. The conclusions of the study focused the attention on the family's (mother's) responsibility that has to encourage and support children practical and emotional regarding the implementation and maintainance of oral hygiene habits.

METHODS

WHO sets accent on on the growth of the sanogen attitudes knowledge level in the population regarding, as well as the action on risk factors [19]. This strategy is also taken into consideration in the dental medicine field. In the past, the patient/sanogen education relationship had the cognitive model as a base, where information that had to be transmitted was most important and not the change of behavior. Nowadays the goal is to influence individuals to control and modify their behaviour in order to improve their health and, by default, their quality of life. Starting from the observations and conclusions of the National Ore-dental Prevention Program, we conceived and applied, with the help of students from the Faculty of Dental Medicine in Timisoara, a pilot study, called Ore-dental Health Education in Children - eDentalCare – which has as a starting point the premises that information and knowledge can set

the base for primary and preprimary prophylaxis, based exclusively on the high information level of children, according to to the WHO objectives and strategy to increase the education level of the population. Therefor we designed a program for prevention through education which respects the principles and objectives of a primary prophylaxis program: We have choosen as the primary vector of deployment the school, because it represents the ideal place to promote health, because the educational message doesn't reach only children but also their parents, the school employees and the community as a whole. On the other hand, the Faculty of Dental Medicine has a moral duty to teach students and future doctors, the human side and to make them responsible for individual and group education, as future creators of sanogen behaviours. Oral health education can be taught as a separate topic or included into several topics. For example, children can learn concepts about oral health in biology classes, nutrition classes, environment classes, can write essays on this subject or can learn how to search for informations concerning oral health on the internet.

Informations from the Mass-media also offer a strong channel to broadcast educational and sanogen behavior messages. Education towards physical and psychic health helps pupils to develop healthy attitudes and habits, to accumulate knowledge that will lead them to a sanogen behavior. This initiative is based on the principles of the Ottawa Cart for health promotion and the WHO recommendations for Education and Health Promotion in Schools.

The eDentalCare program had the following protocol:

1. Establishing a collaboration agreement with the School Inspectorate
2. Establishing a collaboration agreement with the management of several kindergartens (4 from the urban area, 2 from the rural area)
3. Establishing a collaboration agreement with child protection institutions: the child protection home and school part of the Rudolph Walter Foundation (Timisoara), Caritas Foundation (Ciacova), "Hansel and Gretel" foster home (Buzias), "For You" Foundation (Timisoara)
4. Establishing the collaboration agreement with 10 schools from Timisoara (urban area)
5. Establishing a collaboration agreement with 3 schools from the rural area (Foeni, Ciacova, Bulgarus)
6. Establishing financing agreements with the company COLGATE
7. Gathering informations about schedules at schools (administration classes or health education classes)
8. Coordinating the school schedule with the student's and the medical staff's schedule
9. Preparing questionnaires, to establish the children's level of information
10. Preparing informational and educational materials according to specific communication and language standards.
11. Establishing a minimal informational amount necessary for each type of educational material, puting theoretical information and practical demonstration together, using interactive games and specific standardized images.
12. Establishing a professional language that is easy to understand consisting of informations specific for each age group with different dificullty degrees, being enunciated in a facil common language.
13. Designing electronic formats that are attractive and friendly, so that the presentations point out necessary informations, and attract attention.

Informations have been systematized, according to specific development stages in children, nature of risk factors and the understanding capacity of children.

Age	Subject	Materials	Place of the presentation
0– 5 years	Informing parents about the child's diet, dental hygiene, baby bottle caries, dental trauma, decidual teeth and prophylaxis of dental conditions.	Picture brochures, posters, video documents which prove stages of tooth eruption, hygiene techniques	Baby nursery, kindergartens
6-9 years	Diet, oral hygiene, appearance of permanent teeth, function and structure of teeth, dental trauma, caries risk factors (dental plaque, smoking, drugs, dento-maxillary anomalies), prophylactic methods.	Videodocuments, oral health demonstrations, animated movies, books, games, internet.	Schools, boarding school, afterschool programs.
10-12 years	Food pyramid, dental caries, dental plaque, self examination, initial caries and selfdiagnose, prophylactic methods, anomalies and addictive habits, prevention, minimal invasive treatment, implications and compliations of early tooth loss.	Videos, projections, documentaries about loss of teeth, treatment of simple and complicated carious lesions, hygiene techniques, internet.	Schools, boarding schools.
12-18 years	Explaining the conexion between oral health and general health, esthetic implications of oral health, oral health and quality of life, implications of health on social and professional development of the individual. Food pyramid, dangerous substances, drugs, medicines.	Documentaries, videos, internet surfing, individual and group programs.	Schools, scientific clubs, special sites of the project specialized on health.

Children who took part in the project have been evaluated taking into consideration the level of information concerning oral health through questionnaires before the program's start and after 3, 6 month, 1 year and 2 years after the project's end. Educational materials have been presented in kindergartens and schools with help from the students from the Faculty of Dental Medicine in Timisoara, in electronic format, for a period of 24 month (2007-2009).

RESULTS AND DISCUSSIONS

In our country one can still observe many deficiencies in the field of oral health. A big part of the population isn't still aware of the necessity to maintain good oral health. It is true that people who live in urban areas have a better oral health status due to their living conditions, but in the rural area there still are many defficiencies. A very important role in educating the people to maintain good oral health plays the acces to information on this topic. Oral health programs offer professional education to prevent and treat dental disease using the internet, brochures and flyers. A educated child who wants to maintain good oral health will form habits that will last all his life and then transmitt them to the next generations. The role of these programs is to make children aware of the benefits of good oral health and of the problem that can appear if oral health is neglected even affecting the general health status, the general look of the individual, his integration into society and his whole life. Untreated dental problems can have severe consequences not only on oral health but also on the entire body. Therefor, many times, the oral health status shows the general status of the organism. Dificitary oral health is the cause for low school performances, bad social relationships and lack of success in life. Pupils with dental problems can not focus, are often distracted and do not do their homework well. If left untreated, dental conditions can lead to deficiencies in nutrition, speech and learning. A child with dental problems has often problems because of absences, social integration at school, but when dental problems are resolved his performances rapidly improve. Persons with deficiencies in their dentition limit their food choice because of chewing difficulties leading to an inadequate diet affecting the physical and psychic development of the child. Inadequate nutrition affects children's school activities, behavior and focusing capacity. The children evaluation questionnaires have been divided in order to obtain informations from 4 major areas: personal data, knowledge level and current practices, information sources about ore-dental health. Questions 1-4 regarded personal data, questions 5-7, 9-11, 13,15,16, current practices. Questions 8, 12, 14, 17-31 targeted knowledge about oral hygiene and dietary habits and questions 32-37 contained informations about the information sources. After the first evaluation, children participated to presentations and educational informing lessons learning about how to maintain their oral health status, being afterwards reevaluated after 6 month and 1 year. After the questionnaire had been returned, it was numerically coded and processed by software that introduced the numerical data in a table (Excel 2002, Microsoft®) in order to obtain an ASCII codification used for statistical calculation and inductive analisys. During the educational lessons children were shown film and projections containing general informations about teeth, dental conditions, their causes, dental hygiene. An important part of the lessons is represented by the children's instruction to practice good dental hygiene. To achieve this goal, flyers and posters have been shown to exemplify brushing techniques and they have also been directly explained on models. We tried to make these lessons interactive, children having the possibility to actively participate, showing us what they know, so that we could make adjustments and they can ask questions about the problems

they have. We had a discussion with the children about an issue wich is very common in our country, namely the visit to the dentist and the fear towards the dentist. This is an important problem because parents are sometimes not well informed and children suffer getting into their teenage years with problems that are much more difficult to treat. After the evaluation one could observe a certain difference between schools from the urban and rural area regarding informations about oral hygiene. Children living in urban areas have more informations than the ones living in rural areas but one can see an important improvement compared to the last years. This is due to the fact that a bigger part of the rural population has acces to mass-information: TV, radio, internet, along with the increasing of the living standards. What the television is concerned, an important role is played by the national campaines of big companies who produce oral hygiene products. Therefor, even children coming from rural areas can watch publicity spots that promote certain products and encourage people to keep their teeth cleen and in a better shape. There still are problems and differences due to economic deficiencies that can be observed in the rural areas in certain parts of the country with declined economy, where families have very low income.

One can observe differences regarding the frequency of dental brush changing, the quality of dental hygiene products, disfavouring children from the rural area, but also what visits to the dentist are concerned. We have to also stress out the fact that, in the urban area, parent's supervision of oral health is more rigorous than in the rural area, so that we can say that it is very important that parents are also being informed to supervise their children.

RESULTS

1. The great importance of oral health programs, taking into consideration that results are obvious benefic aspecially what children are concerned which we help to improve their health in general and their oral health in particular.
2. The way the community gets involved in resolving oral health problems and informing the community is also very important. Better results have been seen in areas where the local authorities collaborated with the Health Ministery and the big oral hygiene producers organizing preventive oral health actions.
3. It becomes more and more obvious that it is necessary to collaborate with the Health Ministry and the Schools Ministry to organize oral hygiene programs in schools and even teach special topics as part of the curricula. Likewise, teachers and educators have to be well informed and instructed to transmit their knowledge to the pupils.

CONCLUSIONS

1. Because the majority of oral conditions can be prevented, effective ways of abordation are necessary to prevent them and promote oral health at community level.
2. A successful preventive program has to address the society in order to have the biggest impact.
3. The implementation of any oral health program has to be realized according to a well thought plan of action, which identifies necessities, establish objectives and resources (human and financial).
4. The center of a school program has to be the child and his family.
5. The implementation of a school program needs the existence of partnerships in the target group (children, parents, guardians) and other factors that are implicated in the program (school personell, dental practices in school, local decision makers).

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VENTRICULAR ARRHYTHMIAS DURING 24 H AMBULATORY ECG RECORDING

ELENA ARDELEANU[1], MOHAMAD IDLBI, DANIELA GURGUS[1], IOANA PURICEL, BORIVOI DRASCOVICI, ELEONORA BURCĂ, GRIGORESCU DELIA, ADRIAN GRUICI, SHAMSA BAAJ, ESTERA GÂLCA

[1] University of Medicine and Pharmacy "Victor Babes" Timişoara

Correspondence to:

Prof. dr. Ardeleanu Elena, tel. 0256.49.29.19, 0729.95.96.16, Email : ardeleanu.elena@clicknet.ro

ABSTRACT

The objective of the study was to evaluate the incidence, prognosis and risk factors of ventricular arrhythmias during 24-h ambulatory electrocardiographic registration in a sample of men between 50 and 60 years, with and without signs of cardiovascular disease.

Methods: The study cohort consisted of 59 patients with or without coronary heart disease, who presented on 24 h ambulatory ECG registration ventricular arrhythmias. They all had non-invasive examinations of leg and carotid arteries. In a logistic regression, factors as smoking, hypertension and diabetes mellitus were significant and independent determinants of frequent or complex arrhythmias in men with coronary heart disease. High alcohol consumption was associated ventricular arrhythmias in men without CVD.

Conclusion: Ambulatory ECG recording is a diagnostic method that improves risk assessment in men with CVD. Complex ventricular arrhythmias were associated with smoking, hypertension and diabetes mellitus.

Key words: Incidence of ventricular arrhythmias-ambulatory ECG recording- risk factors-cardiovascular disease

INTRODUCTION

Studies with ambulatory electrocardiographic recordings have documented episodes of frequent and complex ventricular arrhythmias at the elderly people with coronary heart disease, but also in apparently healthy persons. In subjects with coronary heart disease mortality depends on cardiac arrhythmias. Atherosclerotic leg (PAD) and carotid artery disease (CS), even in asymptomatic stages, are associated with an increased incidence of myocardial infarction (MI) and death. Some studies observed that these ventricular arrhythmias detected on Holter monitoring (1, 2) are associated often with risk factors as hypertension, smoking, carotid disease, but few studies have compared the contribution of these factors in subjects with and without cardiovascular disease.

OBJECTIVES

The objective of the study was to compare the occurrence and the associated risk factors of ventricular arrhythmia in

elderly men with and without symptoms of cardiovascular disease (CVD).

MATERIALS AND METHODS

The study group consisted of 59 elderly men with age between 60-70 years. The study included an examination of cardiovascular history and status, 24-h ambulatory ECG registration, the carotid artery Doppler ultrasonography and the ankle-brachial blood pressure index (ABPI) recording. By means of an interview we assessed physical activity, smoking habits, alcohol consump¬tion, physical activity and medication. The occurrence of ventricular arrhythmia was studied by ambulatory ECG recording during a 24-h period.

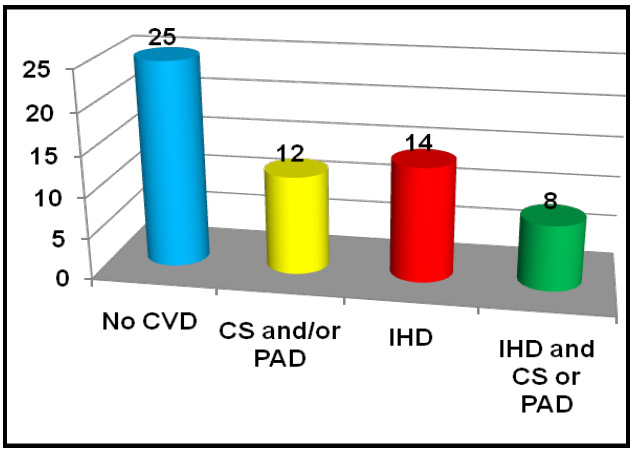

Fig.1. Clinical status of the study group

According to physical activity, we established four groups of patients: 1. almost completely inactive; 2. performing sometimes physical activity; 3. regular activity; and 4. regular hard physical training. On base of physical activity, the patients were divided into the groups 1 + 2 and 3 + 4.

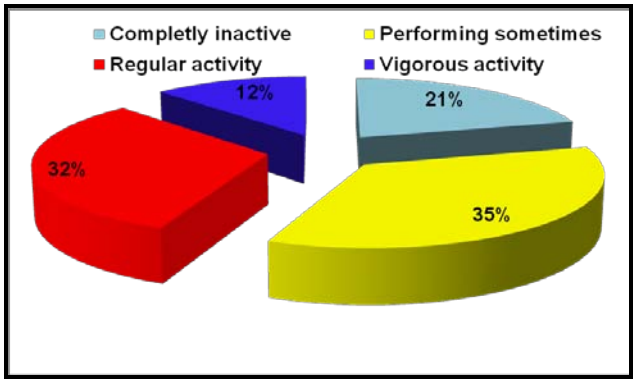

Fig.2. Physical activity of the study population.

Blood pressure was measured in the morning with the subjects in a sitting position. Pressure was measured with a mercury sphygmomanometer and a 12 X 26 cm rubber cuff. Men with systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg were classified as hypertensive. Men who never smoked or who had stopped smoking at least 1 month before the examination were categorized as non-smokers. According to alcohol consumption, men were categorized into

consumers of 250 g alcohol/ week or more and those who drank less than 250 g/ week. Total plasma cholesterol and triglyceride levels were analyzed with standard methods. Total cholesterol concentrations > 200 mg/dl or triglyceride levels > 150 mg/dl were considered as hyperlipidaemia. Blood samples for determination of lipids and glucose were drawn after a minimum fasting period of 8 h. Diabetes mellitus was defined as fasting blood glucose > 126 mg/dl or medication for diabetes mellitus. All cases were validated by hospital records. Borderline cases underwent oral glucose tolerance tests.

Ambulatory 24-h ECG recordings and Lown classification

An electrocardiographic tape recorder (EC-2H Cardiospy) was used with two bipolar electrodes in the V2 and V6 positions. The interpretation of the type of ventricular arrhythmias was made by computer with Cardiax 4.1 soft. In addition, all tapes were analyzed by well-trained doctors. The subjects with cardiac arrhythmias were categorized according to Lown classification. The groups were defined as: grade 0, no ventricular ectopic beats; class 1<720 ventricular extrasystoles /24 h; class 2 >720 ventricular extrasystoles /24 h; class 3, multiform ventricular extrasystoles or bigeminal or trigeminal extrasystoles; class 4a, ventricular extrasystoles in couplets; class 4b, nonsustained ventricular tachycardia; and class 5, ventricular extrasystoles of type R/T. Frequent or complex ventricular arrhythmias were defined as Lown class 2-5.

Ankle-brachial blood pressure index and carotid artery examination

Blood pressure cuffs of 18 X 60 were used to measure ankle pressure and 12 X 35 cm cuffs for the upper arms blood pressure. Duplicate recordings were made and the arithmetic average was used. Periph¬eral arterial disease was defined as a systolic ABPI < 0.9. For carotid artery examination we used an ultrasound device Vingmed 727. Carotid continuous Doppler examination with a maximum frequency shift greater than 3.0 kHz bilaterally or unilaterally (corresponding to a stenosis of more than 30% of the cross-sectional diameter of the artery lumen was considered as having a carotid stenosis. Definition of cardiovascular disease: the presence at least one of the following criterias was considered criteria of cardiovascular disease (CVD): angina pectoris; previous hospitalization because of myocardial infarction or coronary heart disease, positive effort test; ABPI < 0.9; or carotid stenosis. Statistics For analyses of frequencies, Pearson's chi-square with continuity corrections was carried out. The multivariate relationships between a number of cardiovascular risk factors and frequent or complex arrhythmias (Lown class 0-1 vs. 2-5) were calculated by means of logistic regressions method.

RESULTS

The 59 patients of the study population presented different types of severity of ventricular arrhythmias in relation to ischemic heart disease (IHD), carotid stenosis (CS) and peripheral arterial disease (PAD), as presented in table 1. Twenty two patients had coronary heart disease, twelve carotid artery diseases, and 25 showed no evidence of CVD. Arrhythmias of Lown class 2-5 had a lower incidence in men without CVD and in men with carotid stenosis (CS) or peripheral arterial disease (PAD) than in men with ischemic heart disease (IHD). Fourteen patients presented both coronary heart disease peripheral vascular disease and carotid stenosis. The patients with ischemic heart disease, in combination with PAD or CS, had during the registration more ventricular extrasystoles (VES). The number of men who had a history of myocardial infarction did not differ significantly between men categorized as IHD or IHD in combination with PAD or CS.

Table I. Ventricular arrhythmias in relation to IHD, CS and PAD

Clinical status	*Nr (%)*	*History of MI (%)*	*Lown class 0±1 n %*	*Lown class 2±5 n %*
No CVD	25 (42)	0	18 (72)	7 (28)
CS and/or PAD	12 (20)	0	8 (67)	4 (33)
IHD	14 (24)	6 (42)	5 (36)	9 (64)
IHD and CS or PAD	8 (14)	4 (50)	3 (38)	5 (62)

Table II. Characteristics of CVD patients - relation to ventricular arrhythmias

Characteristics	No (%)	Lown 0-1 (%)	Lown 2-5(%)	P-value
Hypertension	12 (54)	6 (27)	6 (27)	NS
Antihypertensive medication		4 (67)	3 (50)	NS
Systolic BP (mmHg)		150.0±21	154.0±23	NS
Diastolic BP (mmHg)		93.0±12	92.4±11	NS
Plasma lipids Hyperlipidemia	7 (31)	4 (18)	3 (13)	NS
Cholesterol -mg/dl		200±20	205±22	NS
Triglycerides mg/dl		150±18	155±19	NS
Smoking habits Never smokers	5 (22)	4 (18)	1 (4)	0.16
Current smokers	17 (77)	7 (31)	10 (45)	0.12
Kalium mg/dl		4.2±0.34	4.4±0.39	NS
Alcohol>250 g week	5 (22)	1 (4)	4 (18)	NS
Vigorous physical activity	7 (31)	3 (13)	4 (18)	NS
Diabetes mellitus	6 (27)	2 (9)	4 (18)	0.01

Table III. Characteristics of patients without CVD - ventricular arrhythmias

Characteristics	*No. (%)*	*Lown 0-1(%)*	*Lown 2-5(%)*	*P-value*
Hypertension	37 (100)	18 (48)	19 (52)	NS
Antihypertensive medication		7 (40)	8 (42)	NS
Systolic BP (mmHg)		152.0±21	153.0±20	NS
Diastolic BP (mmHg)		92.0±12	93.0±11	NS
Cholesterol mg/dl		230±20	234±19	NS
Smoking habits Never smokers	17 (46)	9 (24)	8 (22)	NS
Current smokers	20 (54)	9 (24)	11 (30)	NS
Kalium mg/dl		4.3±0.34	4.22±0.32	NS
Alcohol > 250 g / week	8 (22)	2 (6)	6 (16)	0.02
Vigorous physical activity	11 (30)	5 (14)	6 (16)	NS
Diabetes mellitus	6 (16)	3 (8)	3 (8)	NS

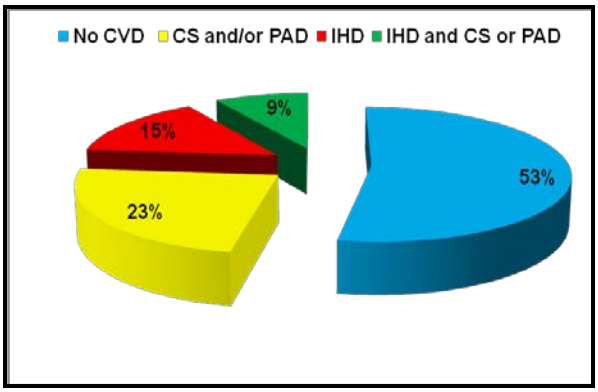

Fig.3. Occurrence of arrhythmias class 0-1 Lown at the study group

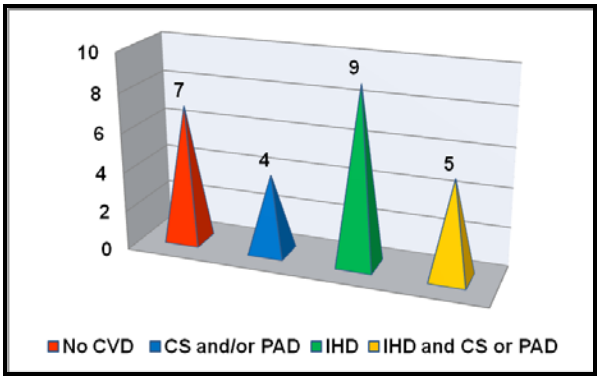

Fig.4. Occurrence of arrhythmias class 2-5 Lown at the study group

Table IV. Clinical status and types of ventricular arrhythmias Lown classes 2-5

Presence of disease	No (%)	Big/Tri [n (%)]	Couplet VES [n (%)]	VT [n (%)]
No CVD	7 (12)	4 (57)	2 (28)	1 (14)
CS and/or PAD	4 (7)	3 (75)	1 (25)	0 (0)
IHD	9(15)	4 (44)	2 (22)	3 (33)
IHD and CS or PAD	5(8)	1 (20)	2 (40)	2 (40)

Big/Tri, bigeminal or trigeminal VES; VT, ventricular tachycardia

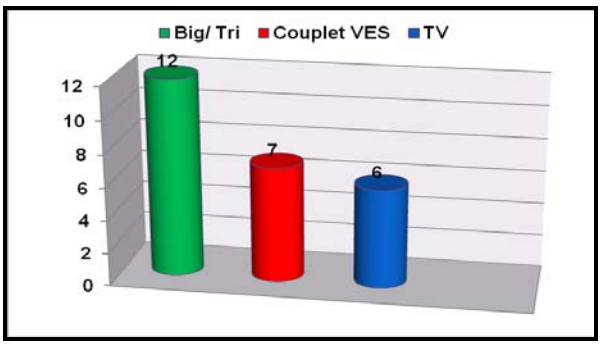

Fig.5. Types of ventricular arrhythmias

The plasma lipid levels and blood pressure showed no significant difference between men with and without frequent or complex arrhythmias. Among men without CVD who had arrhythmias in Lown class 2-5, there were significantly more high consumers of alcohol. Among men with CVD, there was a significant relationship between diabetes and Lown class 2-5. (P = 0.01). With the purpose of exploring the relationships between frequent or complex arrhythmias and various cardiovascular risk factors, alcohol, current smoking, diabetes, hyperlipidaemia, physical activity, hypertension and antihypertensive therapy were introduced in a logistic regression model as independent variables with Lown class 0-1 vs. 2-5 as the dependent variable.

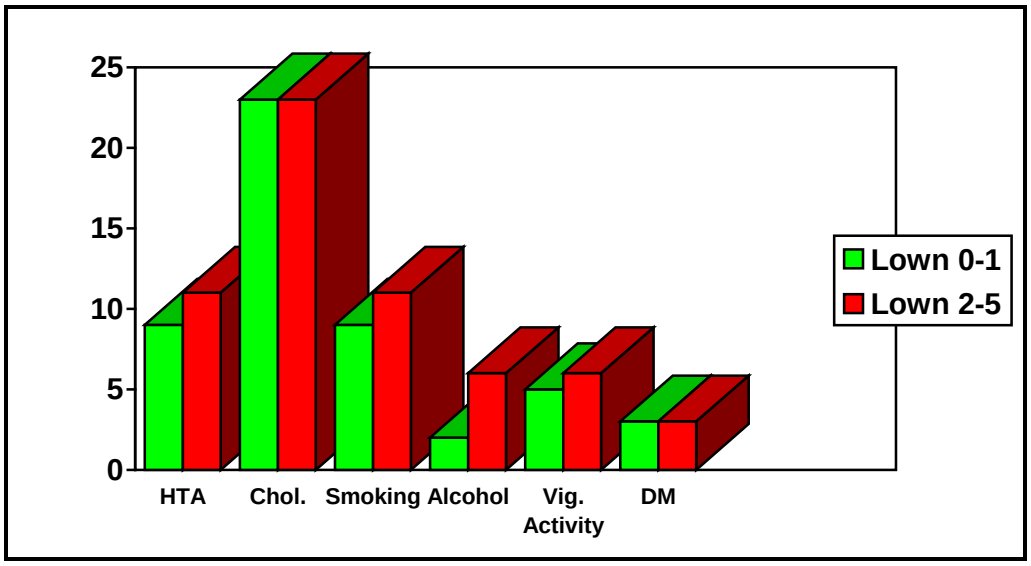

Fig.6. Risk factors present at the patients without CVD

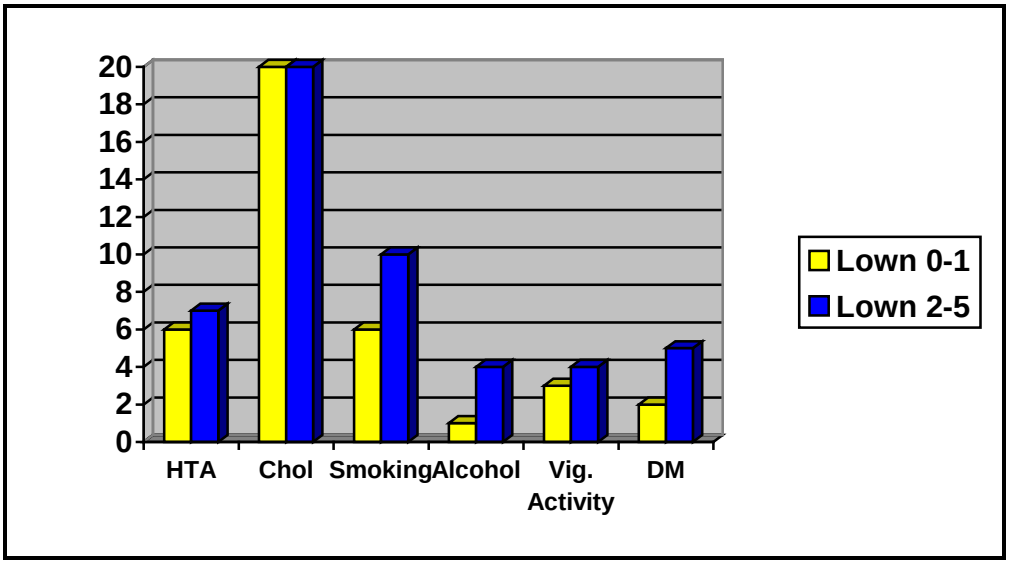

Fig.7. Risc factors present at the patients with CVD

In all men, the presence of diabetes or CVD was independently associated with arrhythmias in Lown class 2-5. In men with CVD, smoking and diabetes were significantly and independently associated with arrhythmias in Lown class 2-5. In men without CVD, high consumption of alcohol was independently related to Lown class 2-5, whereas neither diabetes nor smoking was positively associated with Lown class 2-5.

DISCUSSIONS

Although progression of atherosclerosis is associated with ageing, both the extension and severity of lesions at a certain age may differ greatly between individuals. Almost 42 % of these men of 60 to 70 years had no signs or symptoms of cardiovascular disease. Men with a history of IHD seemed, on average, to have more extended disease. The distribution of known risk factors for atherosclerosis was similar in men with and without cardiovascular disease. The most plausible explanation for this is that in older people, the associations with known risk factors tends to become attenuated or even disappear due to selective premature mortality of risk-exposed individuals. It has been shown in prospective studies that asymptomatic carotid and leg artery disease, even in the absence of a history of IHD, are both associated with an increased incidence of myocardial infarction and death. The occurrence and type of ventricular arrhythmia in men with prevalent atherosclerosis in either the leg or carotid arteries was similar to what was observed in men free from cardiovascular disease. The prognosis with regard to incidence of myocardial infarction was, however, quite different in the two groups. Ambulatory ECG recording should hence be considered a feasible method to improve risk assessment in subjects with asympto¬matic leg and carotid artery disease. Prevalent leg or carotid artery disease seemed to add further risk of ventricular arrhythmia in subjects with a history of IHD. The occurrence of episodes of frequent or complex forms of ventricular arrhythmia in men free from cardiovascular disease had no influence on the incidence of myocardial infarction or death. Alcohol-related deficiency of serum electrolytes and non-athero-sclerotic heart diseases are both possible explana¬tions for the associations between alcohol and arrhythmia (6).

CONCLUSIONS

In subjects with cardiovas¬cular disease, the incidence of frequent and complex forms of ventricular arrhyth¬mia is increased by smoking and diabetes. High alcohol consumption seems to be the major risk factor for the occurrence of ventricular arrhythmia in men free from cardiovascular disease.

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THE MANAGEMENT OF THE OTITIS MEDIA WITH EFFUSION IN THE ENT CLINIC TIMISOARA

FARA L.[1], TOMA ANA-OLIVIA[1], POENARU MĂRIOARA[2], PANAITESCU CARMEN[1], SARĂU C.[1], HORHAT RALUCA[2], HORHAT DELIA[1], STANESE ANA MARIA[2], MOCANU VALERIA[1], HORHAT F.[1]

[1] University of Medicine and Pharmacy "Victor Babeş" Timişoara
[2]Clinica ORL Timisoara

Correspondence to:
Lucian Fara MD, University of Medicine and Pharmacy "Victor Babes" Timisoara, Spl.T. Vladimirescu no.14[a], phone number: 0723886103, email: lucifara@gmail.com

ABSTRACT

Otitis media with effusion (OME) is a pathologic condition of the middle ear in which an effusion is present behind an intact eardrum without signs of acute inflamation.

The authors made a retrospective study on 134 children diagnosed with OME between 2004-2009 in the ENT Clinic Timisoara. In order to establish a diagnosis and a therapeutic conduct, children have been examined by otomicroscopy, audiometry and tympanometry with the testing of the acoustic reflex. When necessary, allergy tests have been added. A study protocol included that all patients benefit fron the treatment according to the aetiology. 74 patients (55.22%) were cured after 21 days following a drug treatment with nasal decongestants and antiinflamatory therapy. For 26 children (19.4%) adenoidectomy was performed due to the fact that repeted episodes of acute otitis media (AOM) and OME were asociated with chronic adenoiditis. For 18 patients (13.43%) antiallergic treatment was prescribed due to the rhinosinusal allergy association. Aditionally, 7 (5%) of these patients were the subjects of adenoidectomy and ventilation tube insertion. Ventilation tube insertion as stand alone treatment was performed on 16 patients (11.94%). However, in spite of the treatment, 10 patients presented refractory OME: 7 patients with medical treatment, 2 patients with grommet insertion and 1 patient with adenoidectomy.

Key words: otitis media with effusion, allergy, tympanostomy, adenoidectomy, grommet insertion

INTRODUCTION

Otitis media with effusion (OME) is a pathologic condition of the middle ear in which an effusion is present behind an intact eardrum without signs of acute inflamation. It results from alterations of the muco-cilliary system within the middle ear cleft and is frequently caused by malfunction of the Eustachian tube. Synonyms commonly used for this lesion are: mucoid otitis media, catarrhal otitis media, tubotympanitis, otitis media with effusion, otosalpingitis, secretory otitis media, non-suoourative otitis media, mucoid ear, mucotympanum, etc. Most of these definitions are inaccurate, however, resulting in misunderstandings on this subject. The term glue ear has been used for the first time in 1949 and in 1946, an

american otolaryngologist, Eagle, from Duke University, North Carolina, described the condition as "the new american disease". Politzer has described a condition which he termed "otitis media catarrhalis". OME is a frequent disease especially in children; between 54-86% of children experience at least one episode of acute otitis media by the age of 2 years. Middle ear effusions occur in up to 90% of children by the age of 2. Refractory OME may associate hearing loss, delay in the acquisition of language, as well as behavioural, developmental and cognitive difficulties. The recent progress in establishing the aetiology of this pathology led to the elaboration of an adapted therapeutical conduct.

MATERIAL AND METHOD

The authors made a retrospective study on 134 children diagnosed with OME between 2004-2009 in the ENT Clinic Timisoara. In order to establish a diagnosis and a therapeutic conduct, children have been examined by otomicroscopy, audiometry and tympanometry with the testing of the acoustic reflex. When necessary, allergy tests have been added. The management plan of the OME included the etiopathogeny establishment for each type of disease: adenotonsilitis, naso-sinusal allergy, rhinosinusitis, gastro-esophageal reflux, congenital malformations, etc. There has been applied a different treatment according the etiopathogeny. The follow-up of the patients was distributed evenly, initially at 21 days, then at 1 month and after that monthly up to 6 months and established the efficiency of the treatment.

RESULTS

The age of the study group ranged between 8 months and 16 years (median age= 4.5). The presenting complaints were: hearing loss in 47.76% of the cases (64/134), otagia in 43.28% (58/134), feeling of fullness in 39.55% (53/134), and popping sensation in 31.34% (42/134) and tinnitus in 6.71% of the children (9/134).

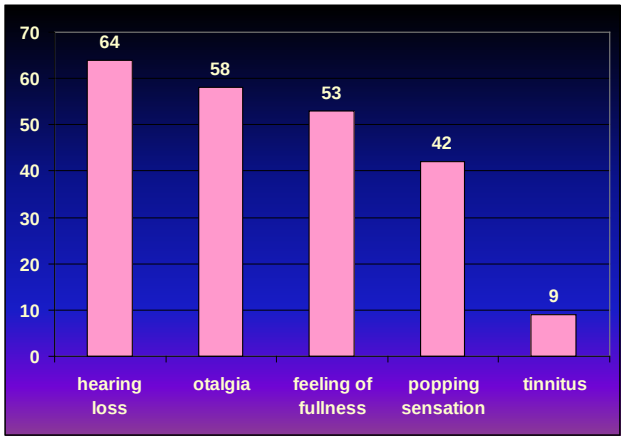

Fig.1 – The presenting complaints in the study group

33 children presented chronic adenoiditis and 18 patients had positive allergy tests. The pure tone audiometry showed mild conductive hearing loss, ranging from 15 to 40 dB hearing threshold level. The apect of the tympanometry was in 47.76% type B and in 44.77% type C. A study protocol included that all patients benefit fron the treatment according to the aetiology. The results are as follows: 74 patients (55.22%) were cured after 21 days following a drug treatment with nasal decongestants and antiinflamatory therapy. For 26 children (19.4%) adenoidectomy was performed due to the fact that repeted episodes of acute otitis media (AOM) and OME were asociated with chronic adenoiditis. For 18 patients

(13.43%) antiallergic treatment was prescribed due to the rhinosinusal allergy association. Aditionally, 7 (5%) of these patients were the subjects of adenoidectomy and ventilation tube insertion. Ventilation tube insertion as stand alone treatment was performed on 16 patients (11.94%). However, in spite of the treatment, 10 patients presented refractory OME: 7 patients with medical treatment, 2 patients with grommet insertion and 1 patient with adenoidectomy.

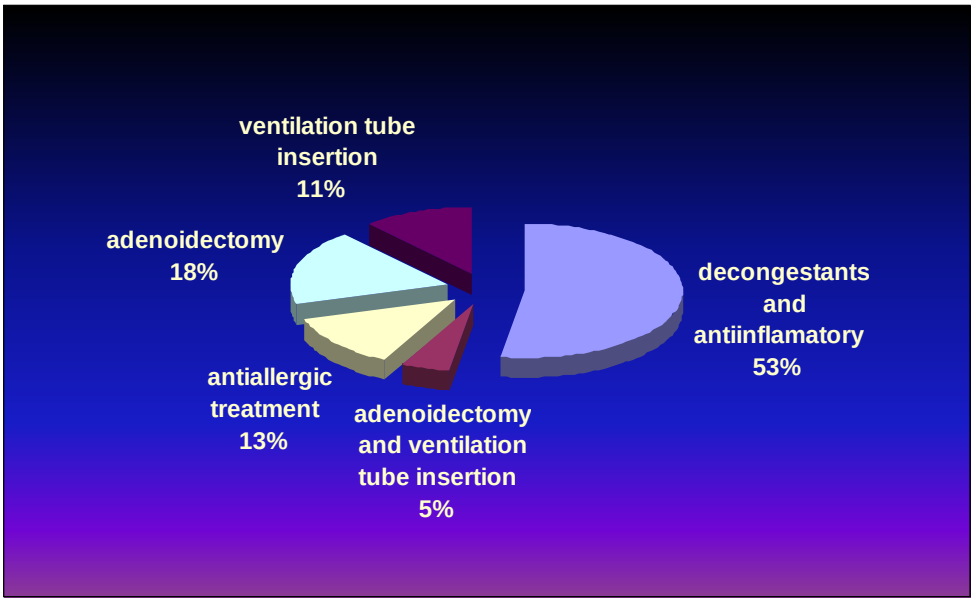

Fig.2 – The therapeutic attitude in the study group

1 patient presented minor bleeding after the adenoidectomy and 2 patients needed to repeat the myringotomy because of the repeated OME after the removal of the grommets.

DISCUSSIONS

OME is characterised by the presence of a fluid in the tympanic cavity containing inflamatory and collumnar cells. The condition involves the Eustachian tube, the middle ear and the mastoid, through the additus ad antrum. Neutrophils, macrophages and lymfocytes (B and T lymfocytes) are the predominant cell types in the middle ear catarrhal effusion; monocytes and phgocytes are present, but in small numbers; eosinophils, mast cells, basophils and plasma cells are rare. The cuboidal epithelium of the middle ear undergoes a progressive metaplasia and transition to a columnar cilliated epithelium with numerous secretory goblet cells. Submucosal inflamatory cells are present in the mucoperiosteum. Ig A and Ig G have been demonstrated using immunofluorescent staining of mononuclear cells from middle ear effusions. Ig M and Ig E have been detected infrequently. The fluid present in the middle ear may be yellowish or dirty gray and becomes dense. Inflamation dammages the epithelium and paralyses cilliary motility, and the mucous secretions are detained in the middle year. They may accumulate and impair clearance and drainage functions. In children, by far, the most common type of effusion seen in practice is the mucoid one, while the serous type is less frequent. In this multifactorial disease, the risk factors are divided into host, environmental and aetiologic factors. Host factors include race, gender, Down's syndrome, Kartagener's syndrome, cleft palate, early onset of otitis

media, respiratory tract infections, adenoids and exceptionnaly nasopharyngeal tumors. Environmental factors include season, bottle-feeding, day care and passive smoking. Aetiological factors include micro-organisms, toxic substances and antigens. The most important cause in the pathogenesis of OME is the abnormal Eustachian tube function, due to anatomical or physiological abnormalities. The importance of Streptococcus pneumoniae, Hemophilus influenzae and Stafilococcus aureus and the increased incidence of infection due to Moraxella catarrhalis have been demonstrated in the etiopathogenesis of the OME. The role of allergy as an ethiological factor in OME is uncertain. In our study group allergy tests have been positive at 18 patients (13.43%). Adenoid tissues from patients from this disease seem to have infectious foci, aggravating immune reactions, which might attack the middle ear via an ascending route. The most frequent complaint is hearing loss, which was present in our study at 47.76% of the children. Other symptoms may be sticking or cracking sound heard on yawning or swallowing, sensation of fullness in the ear, tinnitus, usually low-pitched, pulsating or continuous, mild earache, infection of the upper respiratory tract. The diagnostic protocol should include microscopy and pneumotoscopy, impedance. Pure tone audiometry should be added to measure hearing levels. The hearing impairment due to OME has been found to have negative effects on children's speech and language development, intelligence, educational achievment and behaviour, or social and emotinal adjustment. OME includes many management strategies. The purpose of treatment is to remove the mucous secretion, prevent its reccurence and re-establish the permebility of the Eustachian tube. The medical treatment includes antimicrobial therapy, steroids, decongestants and antihistaminics, mucolitics and tubal insuflation. In our study group the medical treatment with nasal decongestants and antiinflamatory therapy associated with tubal insuflation in older children has been efficient for 74 patients (55.22%), which have been cured after 21 days. Antiallerrgic treatment has been recomanded at 18 patients (13.83%) with positive allergy tests. The surgical treatment consists of miringotomy with grommet insertion, adenoidectomy or adenoidectomy and miringotomy with grommet insertion. The surgical treatment has been necessary in 49 children (36.56%). Miringotomy, tympanostomy and ventilation tube insertion with or without adenoidectomy have been found to reduce conductive hearing loss secondary to middle ear effusion. Issa et all. Found that a significant behavioural change was evident after grommet insertion. Miringotomy was performed in 23 children, in 7 (5%) cases associated with adenoidectomy and in 16 cases (11.94%) as stand-alone treatment.The positive effect of adenoidectomy is to reduce the frequency of otitis media episodes, preventing the subsequent need for ventilation tubes and leading to a long term resolution of chronic middle ear effusion. In the majority of children with chronic middle ear effusion, adenoidectomy removes the underlying reason for reccurent infections in the uuper airways that affect the Eustachian tube function and middle ear aeration. On the other hand, initial grommet insertion without removal of the adenoids exposes the child to all potential risks (surgical intervention under general anesthesia, post-tympanotomy otorrheas) and drawbacks (hampering a child's motor development, since the outer ear canal should not be irrigated with water). Prevention of childhood OME is presumably the most efficient mean to manage it. Preventive measures may include means to improve hygiene in child daycare centers and in other places were young children gather. Vaccination against middle ear pathogens or even against viruses causing respiratory tract infections predisposing to OME is attractive, but currently there is only a restricted set of vaccines available against these pathogens. It is important to protect young children

from inhaled irritants, like tobacco smoke. Studies of the biochemestry of the OME focused on the inflammatory biology of the middle ear and molecular biology tools have recently been applied to the study of otitis media, prompting further research on the treatment and ultimate prevention of this disease.

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COMPARATIVE ANTIMICROBIAL ACTIVITIES OF ANTISEPTIC MOUTHRINSES AGAINST ISOGENIC PLANKTONIC AND BIOFILM FORMS OF ACTINOBACILLUS ACTINOMYCETEMCOMITANS

FINE DH.[1], FURGANG D.[1], BARNETT ML.[1]

[1] New Jersey Dental, School, Newark, NJ, USA; Consumer Healthcare Research & Development, Wamer-Lambert Co., Morris Plains, NJ, USA

Correspondence to:

Daniel H. Fine, Dental Research Center, UMDNJ, MSB. Room C636, 185 South Orange Ave.Newark. NJ 07103, USA

ABSTRACT

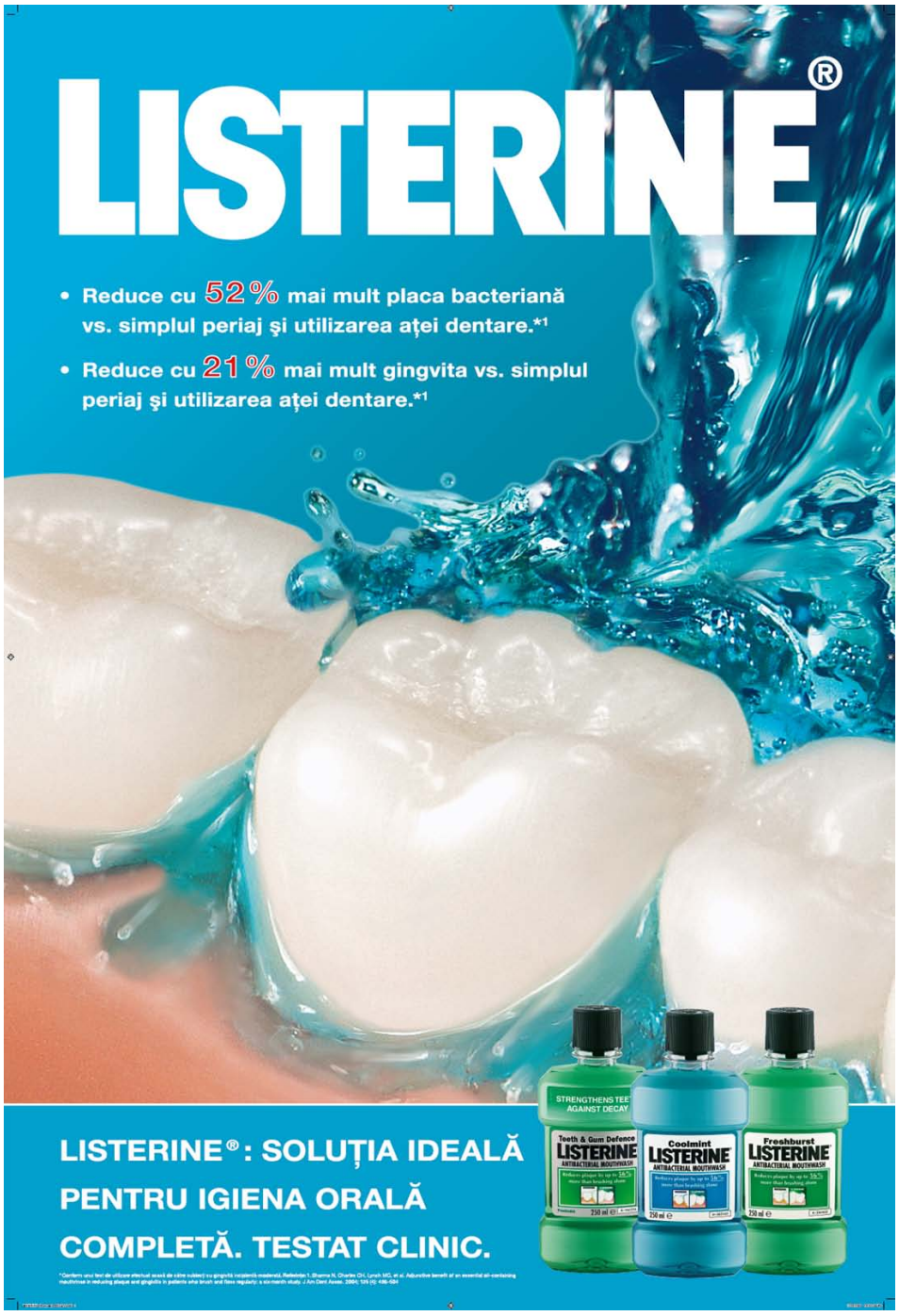
Bacteria contained in biofilms have been shown to have a decreased susceptibility to antimicrobial agents compared to those in planktonic form. Thus, in vitro biofilm models have been developed for screening oral antimicrobial formulations in an effort to produce findings more predictive of clinical activity. This study compared the antimicrobial activity of three mouthrinse formulations when tested against isogenic strains of Actinobacillus actinomycetemcomitans (Aa), one of which was a clinical isolate which forms tenacious biofilms in vitro and the other of which was a spontaneous variant which always grows planktonically.

Key words: antimicrobial mouthrinse; biofilms; in vitro testing; essential oils; amine fluoride/stannous fluoride; triclosan

INTRODUCTION

Biofilm-forming Aa strains CU1000 and NJ4300, obtained as clinical isolates, and their respective spontaneous planktonic variants, CU1060 and NJ4350, were grown under standard laboratory conditions and exposed for 15 s to either a negative control (phosphate buffered saline [PBS)), an essential-oil containing mouthrinse (Listerine® Antiseptic [LA]), an amine fluoride/stannous fluoride-containing mouthrinse (Meridol® [M]), or a triclosan and PVM/MA copolymer-containing mouthrinse (Plax® [P]). The cells were then washed, serially diluted, plated, and incubated for enumeration of viable bacteria. Colony-forming units (CFU)/ml were log 10 transformed and the mouthrinse groups were compared to the PBS group using analysis of variance. Results: All 3 mouthrinses produced statisically significant 99.99% reductions ($p \leq 0.0001$) in both planktonic strains compared to the PBS control. Effects on the biofilm forms of the organisms were more variable.

Exposure to LA produced statistically significant ($p \leq 0.0001$) reductions in strains CU1000 and NJ4300 of 98.20% and 96.47%, respectively, compared to PBS. M and P produced much smaller reductions which were not statistically significant.



CONCLUSIONS

The results ofthis study, in which antimicrobial mouthrinses were tested against biofilm-forming and planktonic strains of the same organism, provide a clear demonstration of the resistance to antimicrobial agents conferred by biofilm formation and provide additional support for employing tests using biofilms to more accurately assess the relative activities of antiplaque agents in vitro.

Studies investigating the effect of antimicrobial agents on bacteria have indicated that considerably different results can be obtained when bacteria are in planktonic form compared to when they are contained within a biofilm (Embleton et al. 1998, Pan et al. 1999). The increased resistance conferred by the biofilm form is

thought to result from a number of factors including phenotypic differences in sessile bacteria compared to planktonic, differential rates of bacterial metabolism at various sites within the biofilm, and matrix inhibition of diffusion of charged antimicrobial agents (Costerton et al. 1994, Costerton & Lewandowski 1997, Gilbert & Allison 1999).

Since in vitro testing of oral antimicrobial formulations, such as mouthrinses, has traditionally utilized assays involving bacteria in planktonic form, it is not surprising that test results did not always correlate with results of in vivo antiplaque trials in which the formulations were confronted with biofilms, rather than suspended organisms (Addy & Moran 1997). Accordingly, in vitro biofilm models have been developed with which to screen oral antimicrobial formulations in an effort to produce findings more predictive of clinical activity (Tanzer et al. 1972, Wilson 1996).

Perhaps the clearest demonstration of a biofilm's effect on an organism's susceptibility to antimicrobial agents could be achieved if the tests were to use a given organism in both planktonic and biofilm form. We have developed a model which uses clinical isolates of Actinobacillus actinomycetemcomitans (A.a.), which form tenacious biofilms in vitro, and spontaneous variants of these isolates, which grow planktonically (Fine et al. 1999a, b). The model, therefore, allows for the assessment of the antimicrobial activity of mouthrinse formulations against these isogenic strains and provides an indication of relative activity against organisms in planktonic and biofilm form. The objective of this in vitro study was to compare the antimicrobial activity of three mouthrinse formulations using the isogenic A.a. model.

2 strains of Actinobacillus actinomycetemcomitans (A a), CU1000 and NJ4300, were obtained as clinical isolates and shown to form tenacious biofilms in vitro. Once isolated, these strains gave rise to spontaneous variants, CU1060 and NJ4350, respectively, which always grew planktonically.

Tests to determine susceptibility to antimicrobial mouthrinses were conducted as follows, with all determinations repeated 6x. For planktonic strains CU1060 and NJ 4350, the concentration of stock cultures of these organisms in AaGM medium (Mandell & Socransky 1981, Slots 1982) was calculated by serial dilution and plating to determine the number of colony forming units (CFU)/ml. 24 h cultures were adjusted to A260=0.8 (approximately 1x109 cells/ml) and cell pellets from 1000 µ1 aliquots were obtained by centrifugation.

1000 µ1 of either a negative control (phosphate buffered saline [PBS]), an essential oilcontaining mouthrinse (Listerine® Antiseptic [LA], Warner-Lambert Company, Morris Plains, NJ, USA), an amine fluoride/stannous fluoride-containing mouthrinse (Meridol®,Wybert GmbH, Lorrach, Germany), or a triclosan and PVM/MA copolymercontaining mouthrinse (Plax® [P], Colgate- Palmolive (UK) Ltd, Guildford, Great Britain) were added to each pellet, and the pellet dispersed by trituration.

After a 15-s exposure, the mixture was centrifuged for 30 s at 14,000xg, the supernatant was aspirated, and the cells were washed 3x in sterile PBS.

After washing, 1000 µ1 of PBS were added to each tube and the mixture was serially diluted, plated on AaGM agar, and incubated for 2-4 days at 37°C in an atmosphere of 10% CO2 for enumeration of viable bacteria (CFU/ml).

For biofilm forming strains CU1000 and NJ4300, biofilms were formed in AaGM medium in 750 ml tissue culture flasks (Fine et al. 1999b).

The flasks were incubated at 37°C in 10% CO2 for 3-5 days and the biofilms washed 3x in sterile PBS. 10 ml of either PBS or one of the three antimicrobial mouthrinses were added to each flask for 15 s, following which the biofilms were washed 3x in sterile PBS.

Following washing, the biofilms were scraped into I ml PBS, dispersed by sonication for 15 s with a Branson sonifier at low power output, serially diluted, plated on AaGM agar, and incubated for 60 h at 37°C with 10% CO2 for enumeration of viable bacteria (CFU/ml).

The mean CFU's1ml were log10 transformed and the mouthrinse groups compared to the negative control group using an analysis of variance.

The results are presented in Table 1. All 3 mouthrinses produced statistically significant 99.99% reductions ($p \leq 0.0001$) in both planktonic strains, CU1060 and NJ4350, compared to the PBS control.

Effects on the biofilm forms of the organisms were more variable. Exposure to LA produced statistically significant ($p \leq 0.0001$) reductions in strains CU1000 and NJ4300 of 98.20% and 96.47%, respectively, compared to the PBS control.

M and P produced much smaller reductions which were not statistically significant. The results of this study, in which antimicrobial mouthrinses were tested against biofilm-forming and planktonic strains of the same organism, provide a clear demonstration of the resistance to antimicrobial agents conferred by biofilm formation. The finding that all three antimicrobial mouthrinse formulations killed virtually all the organisms in planktonic form while having very different activities in killing organisms in biofilm form provides additional support for employing tests using biofilms to more accurately assess the relative activities of antiplaque agents in vitro.

This study also confirms the results of a previously reported in vitro study in which the antimicrobial activity of LA was compared to that of M against both planktonic organisms and biofilms (Pan et al. 1999).

Additionally, the results reported herein for antimicrobial effectiveness against biofilms are consistent with the findings of comparative clinical studies in which LA was found to be significantly more effective than both M(Riep et al. 1999) and P (Moran et al. 1997, Pollard et al. 1997) in reducing dental plaque.

However, since the biofilm model utilized in this study utilizes a homogeneous biofilm which differs from supragingival plaque, a heterogeneous biofilm, its value as an assessment method which is predictive of clinical effectiveness will have to be further confirmed in additional well designed clinical trials.

Nevertheless, this model can be useful for determining the relative ability of antimicrobial formulations to penetrate the biofilm matrix and affect bacterial viability, thereby differentiating antimicrobial formulations with bactericidal activities thought to be of clinical relevance.

Table 1. Effect of antimicrobial mouthrinses on planktonic and biofilm organisms

	CU1000		CU1060		NJ4300		NJ4350	
	Biofilm		Planktonic		Biofilm		Planktonic	
	CFU(SD)*	% kill	CFU(SD)	% kill	CFU(SD)	% kill	CFU(SD)	% kill
PBS	9.17(0.11)	—	8.89(0.05)	—	9.48(0.07)	—	8.88(0.05)	—
LA	7.32(0.08)#	98.20	3.07(0.05)+	99.99	8.01(0.14) #	96.47	3.02(0.12) +	99.99
M	9.09(0.11)	20.00	4.58(0.04) +	99.99	9.45(0.10) +	5.52	4.45(0.12) +	99.99
P	9.14(0.09)	8.00	3.15(0.04) +	99.99	9.46(0.06) +	3.31	2.94(0.03) +	99.99

*Mean (SD) $\log_{10}$-transformed counts following 15 s exposure to test solution.
** % kill compared to PBS control.
# Statistically significant vs. PBS control ($p \leq 0.0001$).
+ Statistically significant vs. PBS control ($p \leq 0.0001$)

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INSTRUCTIONS FOR AUTHORS

The journal publishes general reviews, studies and clinical, epidemiological, experimental and laboratory research, clinical case presentations, papers from the history of medicine, reviews, scientific and technical state-of-the-art articles, medical informations and opinions. Only papers which have not been published or sent for publishing in other journals are accepted. The authors are responsable for the opinions expressed in the papers. The paper must be edited both in Romanian and in English; the English version will be supervised by our collaborator Dana Brehar-Cioflec, MD, PhD; typed on white A_4 paper (fonts - Times New Roman 12, Romanian characters, line spacing 1.5, upper and lower margins 2cm, left border 3cm, right border 2cm) and on CD, DVD or Memory Stick.

Manuscripts will not exceed:

- general reviews: 6-8 pages
- studies and researches: 5-7 pages
- case presentations: 2-4 pages
- reviews, scientific and technical state-of-the-art articles, medical informations and opinions: 1-2 pages.

The paper will be edited according to international editing rules for manuscripts. The title will be written in capital characters and it will be followed by the name and surname of the author (authors), followed by their place of work (place where the paper has been elaborated). Studies and researches will be followed by a brief abstract, followed by 3-4 key-words.

The body of the paper will be structured on the following chapters: introduction, aim, objectives, material and method, results and discussions, conclusions. The references will be presented alphabetically and in conformity to the Vancouver Convention, including:

- for articles: name of the authors and surname initials, title of the article in the original language, title of the journal according to the international abreviation system, year of issue, volume, number, pages;
- for books: name of the authors and surname initials, volume, publisher (editors), city of publishing, year of issue.

Citation of references inside the body of the paper will be put between brackets, Harward style (author, year) or Vancouver style (number in square brackets or superscript). Cited reference titles will be selected, maximum 6 for studies and case presentations and 12 for general reviews.

Acceptance, rejection or the need of alterations in sent materials, or in inconography, will be comunicated to the authors in due time. For this, the authors will indicate the person and address for corespondence (phone number, e-mail address). Given the less pleasant experience of the editorial board with some articles being rejected because they did not meet publishing criteria, we decided to support those who intend to publish in this journal by detailing the way such a paper should be elaborated, as well as our requirements.

Except some particular aspects concerning this journal, the following details are general requirements asked or imposed by other journals as well. Conditions to be met in order to propose a paper for publishing. The main author has the responsability to make sure the article has been approved by all the other authors. The journal will have copyright for papers accepted for publishing. The editorial board reservs the right to change the style and dimensions of an article (major changes will be discussed with the main author) and to decide the date of issue.

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The editorial board will not consider a paper already reported in a published general review or described in a paper proposed to or accepted by another journal. This does not exclude papers which have been rejected by other journals. Also, papers which have been presented at a scientific meeting will be accepted for discussion if they have not been entirely or partially published in a similar publication.

„Multiple" publishing of the same study is seldom justified. One of the possible justifications is publishing in a second language but only if the following conditions are met:

- Editors of both journals involved are fully informed;
- Priority of the initial publication will be respected by a minimum publishing interval of two weeks;
- For the second publication, a shortened version will suffice;
- The second version strictly reflects data and interpretations in the first;
- A footnote may state: „This article is based upon a study initially published in [title of the journal]".

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Paternity must reflect the common decision of the coauthors. Each author must have participated enough to take public responsability for the content.

A paper with collective paternity must have a key person responsable for the article.

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In order to reproduce materials from other sources, written agreement from the copyright owner must be obtained:

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5. ETHICAL ASPECTS

Do not use name of patients, initials or hospital observation charts numbers. If a photograph of a body part which could allow direct or deductive recognition of the

patient needs publishing, then the paper must be accompanied by the written consent of the patient and clinician, as well.

6. PRESENTING THE MANUSCRIPT

For the journal *„Medicine in evolution"*, the manuscript must be typed double spaced, on white A_4 paper – 210 x 297mm, on one side (2.5cm upper and lower borders, 3cm left and 2cm right border, respectively), in clear characters, no further corrections or addings. It is advisable that articles are presented on CD or other data transfer methods, in Word format, 12 Times New Roman fonts - using Romanian characters – respecting the same page order, accompanied by a printed version. Graphs – black and white or coloured – may be generated in MS Excel or MS Graph, inserted in the body of the paper or presented in a different file.
Infected materials will not be used.

6.1. FIRST PAGE (TITLE PAGE)

Together with the title and names of the authors, the first page must include the affiliation, professional and university degree (if applicable), marked by asterisc for every author; it is advisable to give at least a phone and/or fax number or e-mail address of the first author who may be contacted by the editors for additional recommendations or explanations.

6.2. ABSTARCT OF THE PAPER

6.2.1 Recommendations for original studies

Original studies must include a structured abstarct of maximum 150 words, containing the following titles and informations:

- Aim and objectives;
- Material and methods;
- Results;
- Conclusions;
- Key words: give 3-5 key words;
- The abstract will be translated into an international circulation language.

6.3 CONTENT OF THE PAPER

6.3.1 For original articles

The text will usually be divided into sections:

- Introduction – presentation of general aspects, in the context of the approached theme
- Aim and objectives – Define the aim of the article. Briefly expose the rationale of the presented study or observation. Make strictly pertinent referals and do not exhaustively review the subject. Do not include data or conclusions from the paper.
- Material and methods – Describe the selection of observations or subjects for the experiment (including controls). Identify methods, equipments (with the name and address of the manufacturer in brackets) and give sufficient details on procedures. Give references for the selected methods,

including statistical methods; offer details and brief descriptions for previously published methods which are not well known; describe new or substantially modified methods, justify their use and assess their limitations. Precisely identify all used drugs and chemicals, including generic names, dosage and administration ways. Describe statistical methods with sufficient details for reported results to be verified. Whenever possible, quantify discovered aspects and present them with appropriate measurement indicators for the uncertainty or error of measurement (such as confidence intervals).

- Results – Present results in a logical succession as text, tables and illustrations. Emphasize or briefly describe only important observations.
- Discussions – Underline new, important aspects of the study. Do not repeat in detail data which have been presented in previous sections. Include implications of revealed aspects and their limitations, including implications for future studies. Connect your observations to other relevant studies. Relate the results to the aim proposed for the study.
- Conclusions – organize conclusions which emerge from the study. In the end state: a) contributions to be acknowledged but which do not justify paternity right; b) thanks for technical support; c) thanks for financial or material support.

6.3.2 Indications for case reports

Themes may be selected from all medical fields. Manuscripts which offer a special gain for daily activity will have priority. The title must be clearly, precisely stated. It may be completed by a subtitle. It is advisable to include in the key words of the title the main message, the special element which may be observed from the case evolution. The content of a case report must be divided into three parts:

- Introduction – It must include a maximum of 15 typed rows (half page). Here, the main medical problem is summarized in order to place the case in a specific domain.
- Case report – It contains essential specific information on the case.
- In order to make a logical, chronological and didactical case report the following 5 chapters are needed:

  I. Anamnesis;
  II. Clinical examination data;
  III. Laboratory data;
  IV. Additional paraclinical investigations;
  V. Treatment and evolution.
- Discussions – The reason for the case report must be stated. The report must be patient-centered. Occasional deviations from typical (characteristic) evolutions, nosologically important facts must be presented in such a manner to expose the clinical picture as completely as possible. The case report must not appear as an appendix of a general review. Dimensions of a case report: maximum 6-8 typed pages, 30 rows of 60 characters/page.

6.4. MEASUREMENT UNITS, SYMBOLS, ABREVIATIONS

All measurements must be expressed in International System (IS) units. Abreviations must be fully explained when first used.

6.5. TABLES

Tables are noted with Roman figures and they will have a brief and concise title, concordant with their content.

6.6. ILLUSTRATIONS

Number all illustrations in Arabic figures in a single succession. Apply a label on the back side of every illustration, containing its number and an arrow indicating the upper side. Coloured illustrations may be accepted but it is the choice of the editors, according to particular technical abilities of each journal issue, or it may involve a fee in special cases.

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Offer glossy, good quality photographs. Any annotation, inscription, etc. must contrast with the ground. Microphotographs must include a scale marker.

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Include explanations for each used symbol, etc. Identify the printing method for microphotographs.

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A numbered list of references must be provided at the end of the paper. The list should be arranged in the order of citation in the text of the publication, assignment or essay, not in alphabetical order(according to the Vancouver rules). List only one reference per reference number. It is very important that you use the correct punctuation and that the order of details in the references is also correct.

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